FORMULATION AND EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF TRIMETAZIDINE DIHYDROCHLORIDE.

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LIST OF ABBREVIATIONS

ER	Extended Release
IR	Immediate Release
%	Percentage
Hrs	Hours
Min	Minutes
ml	Milliliter
µg	Microgram
g	gram
g/cm^3	gram per centimeter cube
mg/ml	milligram per milliliter
µg/ml	microgram per milliliter
µm	micrometer
M	Molarity
N	Normality
mg	Milligram
nm	Nanometer
Conc.	Concentration
HPMC	Hydroxy Propyl methyl cellulose
Temp	Temperature
NMT	Not more than
NLT	Not less than
Wt	Weight
Std	Standard
No	Number
i.e.	That is
^0C	Degree Celsius
UV	Ultraviolet/visible spectrometer

CONTENTS

IP	Indian Pharmacopoeia
USP	United States Pharmacopoeia
w/v	Weight by volume
w/w	Weight by weight
v/v	Volume by volume
eq	Equivalent
QS	Quantity sufficient
LOD	Loss on drying

1. INTRODUCTION

1.1. Immediate release (IR) dosage forms

Immediate release dosage forms are conventional dosage forms that allow the drug to dissolve in the gastrointestinal tract with no intention of delaying or prolonging the drug dissolution or absorption. Specifications regarding dissolution characteristics of immediate release dosage forms indicate that at least 85% of the drug should be dissolved in a 60 minutes (Karim Amigh et al., 2006).

Some Limitations of Immediate Release Dosage forms

- In conventional oral dosage forms, there is little or no control over the release of the drug and effective concentration at the target site can be achieved by intermittent administration of glossy excessive doses.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the Gastrointestinal tract, Gastrointestinal motility and so on.
- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult (Chein, Y. W. 1992).
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.2. Sustained Release Dosage Forms

Sustained release technologies can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. Furthermore, the possibility of repeating successful drugs, coupled with the increasing expense in bringing new drug entities to market, has been instrumental in generating interest in sustained-release dosage forms (R.K.Khar & S.P.Vyas, 2002).

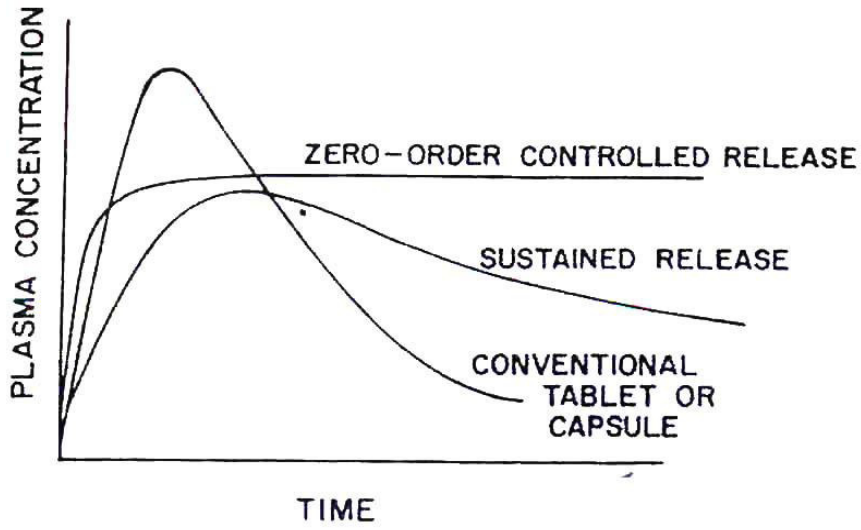
The aim of oral sustained release dosage forms is to achieve a prolonged therapeutic effect by continuously releasing medicament over an extended period of time after administration of a single dose. Sustained release constitutes any dosage form that provides medication over an extended time period. In general, the Sustained release dosage form is to maintain therapeutic blood or tissue level of drug for a prolonged period usually accomplished by attempting slow first order fashion. In recent years sustained release dosage forms continuous to draw attention in the field of research for improved patient compliance and decreased incidence of adverse drug reaction (Rubinstein, M. H, 2000).

The sustained release dosage form is defined as “any drug or dosage form modification that prolongs the therapeutic activity of the drug”. Once the maximum

level is reached, the amount of drug in the body decrease slowly, so it will take longer to drop below the therapeutic range.

The terms sustain or controlled drug release incorporates the element of prolongation of duration of drug action as well as the drug predictability and reproducibility in drug release kinetics. Polymeric sustained drug delivery systems offer numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity, and improved patient compliance (Grass, G. M. & Robinson, J. R, 1990).

Figure 1: Typical plasma drug concentration – profiles for conventional tablet or capsule formulation, a sustained release and an oral controlled release formulation (Kewal K & Jain MD, 2008)**.**



Potential Advantages of Sustained Release Dosage Forms

- Improved patient compliance (Grass, GM, 1990)
- Less frequent dosing (by reducing number of doses).
- Reduced patient care time.

- Decreased local and systemic side effects.
- Reduced Gastrointestinal irritation and other dose related side effects.
- Improved efficiency in the treatment.
- Optimized therapy (Japanese Pharmacopoeia).
- More uniform blood concentration.
- Reduction in fluctuation in drug level and hence uniform pharmacological. response (Robinson, R & Lee, V. H, 1995).
- Cure or control of condition more promptly.
- Reduction in the incidence and severity of untoward systemic side effects. related to high peak plasma drug concentrations.
- Maintenance of the therapeutic action of a drug during overnight no dose period (Lordi, N et. al, 1991).
  - e.g.: Overnight management of pain in terminally ill patient's permits improved sleep.
- Employ less total drug.
- Minimum drug accumulation on chronic dosing
- Economy (Lee, V. H. L et al., 2001).

Disadvantages of Sustained release dosage forms

- They are costly.
- Dose dumping.
- Increased variability among dosage units.

1.3. Matrix devices

Matrix devices consist of drug dispersed homogenously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix (Remington, 2000).

This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system, rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

- A pseudo steady state is maintained during drug release.
- The bathing solution provides sink conditions at all times
- The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
- The diffusion coefficient of drug in the matrix remains constant i.e. no change occurs in the characteristics of the polymer matrix.
- The rate of release of drugs dispersed in an inert matrix system, have been derived by Higuchi's

$$dM = Codh-(Cs/2)dh \text{ ……..... (1)}$$

Where,

dM = Change in the amount of drug released per unit area.

dh = Change in the thickness of the zone of matrix that has been depleted of drug.

C_0 = Total amount of drug in a unit volume of the matrix.

Cs = Saturated concentration of the drug within the matrix.

From diffusion theory,

$$dM = (DmCs/h).dt \text{ ……. (2)}$$

Where

Dm = diffusion coefficient in the matrix.

Equation (1) and (2) integrating and solving for 'h' gives,

$$M= [CsDm (2Co-Cs) t]^{1/2} \text{……. (3)}$$

When amount of drug is in excess of the saturation concentration, that is C_0>>Cs,

$$M= [2\ Cs\ Dm\ C_0t]^{1/2} \ldots\ldots\ldots\ldots (4)$$

Equation (4) indicates that the amount of drug released is a function of the square root of time-

The drug release from a porous or granular matrix can be described by

$$M= (Ds.Ca.\{P/T\}.[2C_0\text{-}PCa]t)^{1/2}$$

Where

P = Porosity of the matrix.

T = Tortuosity.

Ca= Solubility of the drug in the release medium.

Ds= Diffusion coefficient in the release medium.

The system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid filled channels and does not pass through the polymer directly.

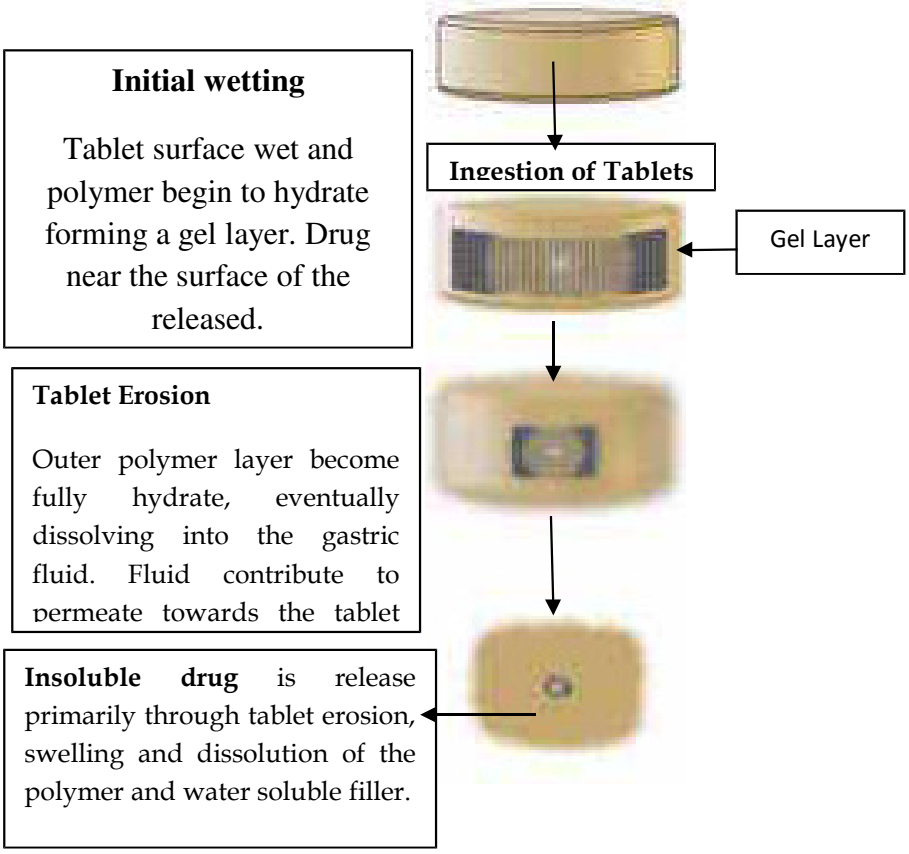
Advantages of matrix diffusion system

- Easier to produce than reservoir devices.
- Can deliver high molecular weight compounds.

Disadvantages of matrix diffusion system

- Can not obtain zero order release.
- Removal of remaining matrix is necessary for implanted systems.

Figure 2: Mechanism of drug release from the matrix tablet.



Physicochemical properties

Aqueous solubility and pKa

A drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. The physicochemical properties of a drug that influence the absorption are aqueous solubility and pKa. These properties play an influential role in the performance of controlled release systems (Remington**,** 2000)

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The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion

across membrane. Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation that under sink condition is:

$$Dc/dt=K_DACs$$

Where,

Dc/dt = Dissolution rate

K_D = Dissolution rate constant

A = Total surface area of the drug particles.

Cs = Aqueous saturation solubility of the drug.

The dissolution rate is constant only if surface areas 'A' remain constant, but, as the initial rate is directly proportional to aqueous solubility (Cs), it can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

Aqueous solubility of weak acids and bases is governed by the pKa of the compound and pH of the medium.

For weak acids,

$$St = S_0 (1+Ka/ [H^+]) = S_0 (1+10^{pH-pKa}) \ldots\ldots\ldots\ldots (1)$$

Where,

St = Total solubility (both ionized and un-ionized forms) of the weak acid

S_0 = Solubility of the un-ionized form

Ka= Acid dissociation constant

H^+= Hydrogen ion concentration of the medium

Equation (1) predicts that the total solubility, 'St' of a weak acid with a given pKa can be affected by the pH of the medium.

For a weak base,

$$St = S0\ (1+ [H^+]/Ka) = S0\ (1+10^{pKa-pH}) \ldots\ldots\ldots (2)$$

Where,

St = Total solubility (both conjugate acid and free base forms) of the weak base.

S_0 = Solubility of the free base form.

Ka = Acid dissociation constant of the conjugate acid

So total solubility (St), of a weak base with a given pKa can be affected by the pH of the medium.

Extremes in the aqueous solubility of a drug are undesirable for formulation into controlled release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. Formulation of such a drug into a controlled-release system may not provide considerable benefits over conventional dosage forms.

Any system relying upon diffusion of drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it often is quite difficult to decrease its dissolution rate and slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.

Partition coefficient

A drug to show its action must diffuse through a variety of biological membranes that act primarily as lipid like barriers. Apparent Oil/Water Partition Coefficient (K) explains the penetration of drug through the lipid membranes and can be defined as,

$$K=C_0/Cw$$

Where,

C_0 = Equilibrium concentration of all forms of the drug e.g., ionized and unionized in an organic phase at equilibrium.

Cw = Equilibrium concentration of all forms in aqueous phase.

Drugs with large values of 'K' are very oil soluble and will partition into membrane readily. According to Hansch correlation, the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient having parabolic relationship.

The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity.

The Partition Coefficient value should be optimum for effective permeation and better activity. The value of K at which optimum activity is observed is approximately 1000/1. Drugs with K value, which is higher or lower than the optimum, are poorer candidates for formulation into controlled-release dosage forms.

Drug stability

One important factor for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution, it is possible to improve the relative bioavailability of a drug that is unstable in GI tract by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach, the most appropriate controlling unit would be one that releases its content only in the intestine. For those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein binding nature of a drug plays significant role in its duration of therapeutic effect. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a controlled–release dosage form. Drugs some times may bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

Molecular size and diffusivity

Drugs in many controlled-release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through membranes, it is so called diffusivity, (diffusion coefficient), is a function of its molecular size (or molecular weight). It is possible to relate log D empirically to some function of molecular size as.

$$\text{Log } D = - Sv \log V + Kv = - Sm \log M + Km$$

Where,

V = molecular volume.

M = molecular weight.

Sv, Sm, Kv, Km = constant.

The value of 'D' thus is related to the size and shape of the cavities as well as size and shape of drugs. 'D' value for drugs with intermediate molecular weight (150 to 400), through flexible polymers range from 10^{-6} to 10^{-9} cm^2/sec, with values on the order of 10^{-8} being most common.

For drugs with molecular weight greater than 500, the 'D' value in many polymers frequently are so small that they are difficult to quantify, i.e., less than 10^{-12} cm^2/sec. Thus, high molecular weight drugs and or polymeric drugs should be expected to display very slow release kinetics in controlled-release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

Biological properties

Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering formulating into a controlled-release system. Since the rate-limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the system is to be successful. This becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorption area of the GI tract is between 9 and 12 hrs, the maximum absorption half-life should

be 3 to 4 hrs. This corresponds to a minimum absorption rate constant Ka of 0.17 to 0.23 hr^{-1} necessary for about 80 to 95 % absorption over a 9 to 12 hrs transit time.

For a drug with a very rapid rate of absorption (i.e. Ka >> 0.23 hr^{-1}), the above discussion implies that a first order release rate constant Kr < 0.17 hr^{-1} is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release systems where the criterion that Kr <<< Ka must be met.

Distribution

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its Apparent Volume of Distribution and the ratio of drug concentration in the tissue to that in plasma at the steady state, the so called T/P ratio. The magnitude of the Apparent Volume of Distribution can be used as a guide for additional studies and as a predictor for a drug-dosing regimen and hence the need to employ a controlled release system.

Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period allowing more complete conversion of drug to its metabolite. Formulation of these enzymatically susceptible compounds as prodrug is another viable solution.

Biological half life

The goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream.

Drugs with short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. But, drugs with very short biological half life require excessively large amounts of drug to maintain sustained effect, forcing the dosage form itself to become large.

Drugs with half-life less than 2 hrs are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already sustained but small dose size of drug can prepare sustained form for reducing there side effect and give prolong action.

Side effects and safety considerations

There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a fall off in desired therapeutic response observed below the range.

TI = TD 50 / ED50

Where,

TD50 = median toxic dose

ED50 = median effective dose.

For potent drugs, the value of TI is small. Larger the value of TI, safer the drug. Drugs with very small value of TI are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

Dose Size

Generally, controlled-release systems will contain greater amount of drug than a corresponding conventional dosage form. For those drugs requiring large conventional doses, the volume of the sustained dose may be so large as to be impractical or unacceptable. The same may be true for drugs that require a large release rate from the controlled-release system, e.g. drugs with shorter half-life and small dose size like 0.5 -10 mg.

Monolithic matrix delivery systems.

These systems can be considered as two groups (M.E. Aulton, 2000).

- Those with drug particles dispersed in a soluble matrix, with drug becoming available as the matrix dissolves or swells and dissolves (hydrophilic colloid matrices)
- Those with drug particles dispersed in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolves the particles (lipid matrices and insoluble polymer matrices)

Lipid matrix systems

The active compound is contained in a hydrophobic matrix (wax) that remains intact during drug release. Release depends on an aqueous medium dissolving the channelling agent, which leaches out of the compact so forming a porous matrix of tortuous capillaries. The active agent dissolves in the aqueous medium and, by way of the water-filled capillaries, diffuses out of the matrix. These matrices are not now in common usage, but the concept is worth considering.

Insoluble polymer matrix systems

An inert matrix system is one in which a drug is embedded in an inert polymer which is not soluble in the gastrointestinal fluids. Drug release from inert matrices has been compared to the leaching from a sponge. The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compacted polymer particles.This type of delivery system would not be suitable for the release of compounds that are insoluble or which have a low aqueous solubility.

Hydrophilic colloid matrix systems

These delivery systems are also called swellable soluble matrices. In general they comprise a compressed mixture of drug and water-swellable hydrophilic polymer. The systems are capable of swelling, followed by gel formation erosion and dissolution in aqueous media. Their behaviour is in contrast to a true hydrogel, which swells on hydration but does not dissolve.

Principle of design of hydrophilic matrices

The system comprises a mixture of drug, hydrophilic colloid, any release modifiers and lubricant/glidant. On contact with water the hydrophilic colloid components swell to form a hydrated matrix layer. This then controls the further diffusion of water into the matrix. Diffusion of the drug through the hydrated matrix layer controls its rate of release. The outer hydrated matrix layer will erode as it becomes more dilute; the rate of erosion depends on the nature of the colloid.

Hydrophilic colloid gels can be regarded as a network of polymer fibrils that interlink in some way. There is also a continuous phase in the interstices between the fibrils through which the drug diffuses. These interstices connect together and are analogous to the tortuous capillaries seen in wax matrices.

The tortuosity of the diffusion path and the 'microviscosity' and interactions within the interstitial continuum govern the diffusion of the drug through the hydrated gel layer, and hence the release of the drug.

Types of hydrophilic matrix

There are two types of hydrophilic matrix systems. They are

- True gels
- Viscous or 'Viscolized' matrices

True gels

These systems interact in the presence of water to form a crosslinked polymeric structure with a continuous phase trapped in the interstices of the gel network. The crosslinks are more than just random hydrogen bonds between adjacent polymer chains (e.g. alginic acid in the presence of di or trivalent cations, gelatin): here they limit the mobility of the polymer chains and give a structure to the gel. The crosslinks can be chemical bonds or physical bonds, e.g. triple-helix formations in gelatin gels which are based on hydrogen bonds. The portions of the polymer chains between crosslinks can move, but the crosslinks restrict the overall movement of the chains.

Viscous or 'Viscolized' matrices

Not all matrix systems form 'true' gels: in reality some are more properly described as very viscous solutions. In the presence of water these systems form a matrix in which the increased viscosity occurs as a result of simple entanglement of adjacent polymer chains, but without proper crosslinking. It is a dynamic structure. The chains are able to move relative to one another and the drug diffuses through the interstitial continuum, but the pathway is not fixed. Examples are hydroxypropyl methylcellulose and sodium alginate in water.

Advantages of hydrophilic matrix systems

- Comparatively simple concept

- Excipients are generally cheap and are usually GRAS (generally regarded as safe)
- Capable of sustaining high drug loadings
- Erodible, so reducing the possibility of 'ghost' matrices
- Easy to manufacture using commonly available equipment, by direct compression, wet granulation or roller compaction
- Well established technology
- Uses readily available pharmaceutical manufacturing equipment
- Possible to obtain different types of release profile: zero order, first order, biomodal etc.

Disadvantages of hydrophilic matrix delivery systems

- Release of the drug is dependent on two diffusion processes, penetration of the water through the hydrated matrix into the nonhydrated core, and diffusion of the dissolved drug through the hydrated matrix.
- If the outer layer of the hydrated matrix erodes, this can complicate the release profile.
- Requires batch-to-batch consistency in the matrix-forming materials, other components and process parameters.
- Scale-up of manufacture can be a problem.
- Need optimal rate-controlling polymers for different actives.

These matrices are comparatively simple in concept. However, the events following hydration can be quite complex. The key is that there are two diffusion processes (water in and then drug out). The drug will only diffuse through a hydrated gel layer. This really only applies to drugs that are solid at room temperature. Liquid

drugs may diffuse in the non-hydrated state and would not be suitable for some types of system.

Components of hydrophilic matrix delivery systems

- Active drug
- Hydrophilic colloids
- Matrix modifier
- Solubilizer and/or pH modifier
- Compression aid
- Lubricant/ Glident.

Those components listed in parentheses are optional and not always necessary.

Matrix-forming agents for hydrophilic matrices

Hydrophilic colloids are which on contact with water form a hydrated gel that remains 'sufficiently intact' during passage through the gastrointestinal tract are suitable matrix-forming agents for hydrophilic matrices.

Examples

Hydroxypropylmethylcellulose,Sodiumcarboxymethylcellulose,Alginates, Xanthum gum/locust bean gum combinations, Carbopol. These agents generally occupy 20-80% of the mass; the actual amount will depend on the drug and the desired release characteristics. Hydration and swelling are the key factors in the functioning of a hydrophilic matrix, as has already been stated.

Gel modifiers for hydrophilic matrix delivery systems

These are materials that are incorporated into the matrix to modify the diffusional characteristics of the gel layer, very often to enhance drug diffusion and hence release of the drug. Examples include sugars, polyols and soluble salts.

The type of modifier will depend very much on the chemical nature of the hydrocolloids used. They may also modify the rate and extent of hydration of the hydrophilic matrix material.Gel modifiers can have a number of other functions.

- To allow more complete, more uniform hydration of the gel matrix
- To allow more rapid hydration of the gel matrix
- To associate with the matrix molecules and thus to influence the interactions at a molecular level, e.g. crosslinking.
- To modify the environment in the interstices of the gel, either to speed up or slow down diffusion.
- To suppress or promote the ionization of ionizable polymers.

Solubilizers and pH modifiers for drugs in hydrophilic matrices

Many drugs will not dissolve sufficiently in gastrointestinal fluids to allow them to be released from a hydrophilic colloid matrix. Dissolution can be improved by the inclusion of solubilizing agents (e.g. PEGs, polyols, surfactants etc.). The only restriction is that the formulation can be formed into a tablet and that the material is acceptable. Many drugs are ionizable. The inclusion of appropriate counter-ions can facilitate release from the system. Some materials can act as both dissolution enhancer and matrix modifier: the amount of excipient needed will be determined by the amount of drug.The above relates to the drug molecule, rather than the matrix material. It is necessary for any drug to be in solution for diffusion to occur. For insoluble drugs, solubilization is therefore an important consideration. With some gel

materials the use of certain ions causes changes in the nature of the gel matrix. The solubilizers and pH modifiers might also influence the release process through a direct effect on the matrix. Different materials could augment crosslinking, whereas others might perhaps weaken the crosslinks.

Lubricants for hydrophilic delivery systems

As with any tablet compacted on a tablet machine, a lubricant is necessary. Lubricants can have four functions:

1. Reduce inter particulate friction during compression and compaction
2. Reduce die-wall friction
3. Prevent sticking to the punches
4. Improve flow of the formulation on to the machine and into the die.

The requirement for lubricants for hydrophilic matrix tablets are no different from those for any other tablet, and are thus analogous to those for conventional immediate-release tablets and capsules. Generally the choice is not governed by the same constraints as in immediate release. For example, over blending or excess magnesium stearate may not be a major problem here. It is not essential that the lubricant is soluble. Such lubricants are available but are generally not very effective and tend to be reserved for effervescent products.

Suitable lubricants to be included in the formulation are listed below.

Hydrophobic lubricants

- Magnesium stearate.
- Calcium stearate.
- Stearic acid.
- Hydrogenated vegetable oil.

Hydrophilic lubricants

- Glceryl palmitostearate
- Glyceryl behenate
- Sodium stearyl fumarate

Drug release from hydrophilic colloid matrices

The classic description of the events following immersion of a matrix in aqueous media is as follows:

- Surface drug (if water soluble) dissolves and gives a 'burst effect'.
- The hydrophilic polymer hydrates and an outer gel layer forms.
- Gel layer becomes a barrier to uptake of further water and to the transfer drug.
- Drug (if soluble) release occurs by diffusion through the gel layer; insoluble drug is released by erosion followed by dissolution.

Following erosion the new surface becomes hydrated and forms a new gel layer.

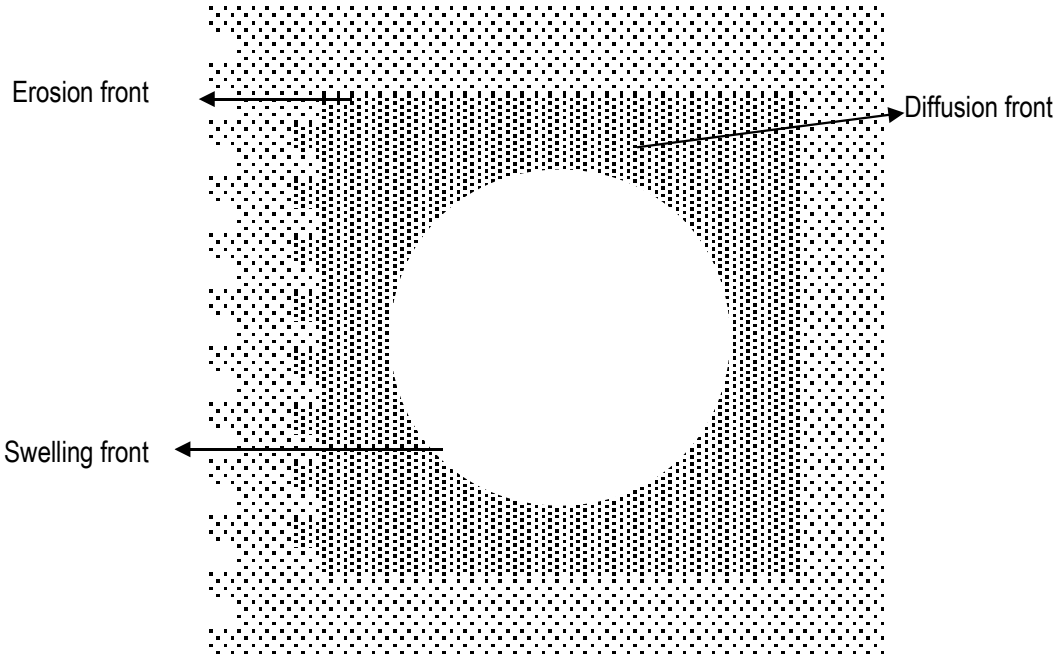
It may be anticipated that the relative importance of each release mechanism will depend on the physicochemical properties of the gel layer; the aqueous solubility of the drug; and the mechanical attrition of the matrix in the aqueous environment.

When a drug/glassy polymer matrix is placed in an aqueous environment, the water penetrates the polymer network. The intake of solvent (water) induces stresses within the matrix polymer. Eventually the matrix polymer relaxes, and this manifests itself as swelling. It is possible to differentiate three 'fronts' during hydration: eroding, diffusing and swelling.

The "swelling front" separates the rubbery region (swelling polymer area) which has enough water absorbed within the polymer to lower the Tg of the polymer below the respective environmental temperature allowing for macromolecular mobility and swelling, from the non-swelling polymer region (where the polymer exhibits a Tg that is above the respective environmental temperature).

The "erosion front" separates the matrix from the bulk solution and is the interface between the unstirred layer with polymer concentration gradient and the well stirred medium. The "diffusion front" is between the swelling and erosion front and separated the areas of non dissolved drug from the area of dissolved drug.

Figure 3: Pattern of drug release from the hydrophilic colloid matrices



The actual drug release mechanism depends on the relative contributions of swelling and dissolution. Drug release from swellable, soluble matrices is constant when swelling and eroding fronts synchronize, but is non-linear when this is not the case.

The release of sodium diclofenac from PVA and from HPMC matrices has been investigated. It was noted that if the fronts synchronized then the gel layer thickness was constant and zero-order release was observed. When synchronization did not take place the gel layer tended to increase in thickness and there was a decrease in the amount released, providing non-linear kinetics.

Matrix tablet.

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of retardant (Lachman L, 1990).

Materials used as retardants in matrix tablet formulations.

There are three classes of materials used as release retardants in matrix tablet formulations viz:

1) Insoluble inert polymers

Tablets prepared from these materials are designed to be ingested intact and not break apart in GI tract. Ingested tablets contain unreleased drug in the core.

e.g. Polyethylene, Poly vinyl chloride, Ethyl cellulose

Methyl acrylate – methacrylate copolymer.

2) Insoluble, erodable polymers

These form matrices that control release through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to the totally insoluble polymer matrix. Total release of drug from

wax-lipid matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films.

e.g. Carnuba wax in combination with stearic acid, stearyl alcohol, Castor wax & Triglycerides

3) Hydrophilic polymers

This group represents non-digestable materials that form gels in situ. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion of the gelled layer. The extent to which diffusion or erosion controls release depends on the polymer selected for formulation as well as on drug: polymer ratio.

Eg: Methyl cellulose, Hydroxy ethyl cellulose, Hydroxypropylmethylcellulose, Sodium alginate.

Types of Matrix Tablets

There are three Types of Matrix Tablets

1. Hydrophilic matrices
2. Fat wax matrices
3. Plastic matrices

1. Hydrophilic matrix tablets

e.g. Sodium Carboxy-methylcellulose, Methylcellulose, HPMC Hydroxylethylcellulose, Polyethylene Oxide, Poly Vinyl Pyrrolidine, Poly Vinyl Acetate, Gelatin, Natural Gums etc.

Several commercial patented hydrophilic matrix systems are currently in use, such as synchron technology and hydrodynamically balanced system.

Advantages

- Ease of manufacture.
- Excellent uniformity of matrix tablet

2. Fat wax matrix tablets

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactants and spray drying techniques.

e.g. Polyethylene, Ethyl Cellulose, Glyceryl Esters of Hydrogenated Resins has been added to modify the drug release pattern.

3. Plastic matrix tablets

e.g.Polyvinyl chloride, Polyethylene, Vinyl Acetate, Vinyl Chloride copolymer, Vinyllidine chloride, Acrylate (or) Methyl methacrylate polymer, Ethyl c ellulose, Cellulose acetate, Polystyrene.

With plastic material(s) tablets can be easily prepared by direct compression of drug provided the plastic material can be communited or granulated to desired particle size to facilitate mixing with drug particles.

Polymers used in Matrix Tablets

The present study focuses on oral controlled-release dosage forms and types of various polymers used to formulate matrix tablets. The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceuticals. Water soluble polymers such as polyethylene glycol and polyvinyl pyrrolidone may be used to increase the dissolution rates of poorly soluble drugs. Hydrogels provide the basis for implantation, transdermal and oral controlled release systems. Hydroxypropyl methylcellulose (HPMC) is cellulose ether which may be used as the basis for hydrophilic matrices for controlled release oral delivery.

Hydrogel

- Polyhydroxyethyle methylacrylate (PHEMA)
- Cross-linked polyvinyl alcohol (PVA)
- Cross-linked polyvinyl pyrrolidone (PVP)
- Polyethylene oxide (PEO)
- Polyacrylamide (PA)

Soluble polymers

- Polyethylene glycol (PEG)
- Polyvinyl alcohol (PVA)
- Polyvinyl pyrrolidone (PVP)
- Hydroxypropyl methyl cellulose (HPMC)

Biodegradable polymers

- Polylactic acid (PLA)
- Polyglycolic acid (PGA)
- Polycaprolactone (PCL)

- Polyanhydrides

Nonbiodegradable polymers

- Polyethylene vinyl acetate (PVA)
- Polydimethyl siloxane (PDS)
- Polyether urethane (PEU)
- Polyvinyl chloride (PVC)
- Cellulose acetate (CA)
- Ethyl cellulose (EC)

Mucoadhesive polymers

- Polycarbophil
- Sodium carboxymethyl cellulose
- Polyacrylic acid
- Tragacanth
- Methyl cellulose
- Pectin

Natural gums

- Xanthan gum
- Guar gum
- Karaya gum

The matrix system is commonly used for manufacturing dosage forms because it makes manufacturing easy. Sustained release tablets are formulated so that the active ingredient is embedded in the matrix insoluble substance. So, that the

dissolving drug has to find its way out through the holes in the matrix. In some sustained release formulation the matrix physically swell up, to form gel, so that the drug has first dissolve in matrix, then exit through the outer surface.

Direct compression.

There are a few crystalline substances, such as sodium chloride, potassium chloride, that may be compressed directly. The vast majority of the drugs are rarely easy to tablet due to poor compressibility and/or flowability. The use of compressible diluents and flow modulators makes this process the most streamlined method of tablet manufacture (Sandip Tiwari, 2003)

Directly compressible vehicles

Definition

A directly compressible diluent is an inert substance that may be compacted with little difficulty and may compress even when quantities of drugs mixed with it.

Compression capacity is still maintained when other tablet materials necessary for flow, disintegration, and so forth are blended in.

Requirements

1) Good flow and compressibility

2) Inert

3) Tasteless

4) Reworkable

5) Able to disintegrate

6) Inexpensive.

Definition

The term direct compression is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients (including filler, disintegrant and lubricants) which will flow uniformly into the die cavity and form into a firm compact. No pretreatment of powder blend by wet or dry granulation procedure is necessary. Occasionally potent drugs will be sprayed out of solution into one of the excipients.

The advantages of direct compression were made possible by the commercial availability of direct compressible tablet vehicles that possess both fluidity and compressibility. The first such vehicle was spray dried lactose, which although it was subsequently shown to have short comings in terms of compressibility and color stability, initiated the "direct compression revolution".

- Lactose monohydrate (pharmatose 200 M, DCL-11, DCL-21 and DCL-25) is the first effective filler.
- Other e.g. Starch 1500; A partially pregelatinized starch that possesses a higher degree of flowability and compressibility. Encompress a free flowing compressible dicalcium phosphate. Nutab, Di–Pac Compressible sugars.

For carrying out direct compression major advantages were made in tablet compression machinery, such as improved positive die feeding and precompression stages that facilitate direct compression tableting.

Advantages

- Economy
  - Reduced processing time
  - Reduced labour time
  - Fewer manufacturing steps
- Elimination of heat and moisture
- Better stability
- Uniformity in particle size
- Good compatibility property.

Disadvantages

- There is need to set functionality specifications on properties such as compressibility and fluidity as well as more traditional physical and chemical properties.
- Not suitable for drugs characterized by high dose, high bulk volume, poor compressibility and poor fluidity.
- Limitation in coloring tablets prepared by direct compression.
- Choice of excipients for their properties is extremely critical in formulating direct compression tablets.
- Direct compression blends are subject to unblending in post blending handling steps. The lack of moisture in the blends may give rise to static charges which can lead to unblending.
- Dust generation is more.

Release from matrix device

Matrix delivery system are of two types diffusion/swellable system, and dissolution system In diffusion systems, drug release is mainly governed by the hydration of matrices, followed by diffusion of drug molecules from the hydrated layer to the surrounding bulk layer of solution, and sometimes, partially by the erosion/dissolution. Examples include Eudragit and cellulose ethers. With dissolution systems, drug release is mainly due to dissolution/erosion of the matrix and hence, achievement of constant drug delivery rate is easier by these systems. Sodium carboxymethylcellulose and natural gums are examples of polymers that are gaining popularity in matrix drug delivery systems.

Drug from matrix may be diffusion, erosion and swelling which may vary molecular size of polymer, nature of polymer, polymer ratio, compounds of polymer etc. have their impact on the release of drug from matrix it may be either diffusion, or erosion and swelling.

Mechanism of drug release from hydrophilic matrix tablets

The mechanism of drug release from hydrophilic matrix tablets after ingestion is complex but it is based on diffusion of the drug through, and erosion of, the outer hydrated polymer on the surface of the matrix. Typically, when the matrix tablet is exposed to an aqueous solution or gastrointestinal fluids, the surface of the tablet is wetted and the polymer hydrates to form a Gelly-like structure around the matrix, which is referred to as the “gel layer”. This process is also termed as the glassy to rubbery state transition of the (surface layer) polymer. This leads to relaxation and swelling of the matrix which also contributes to the mechanism of drug release. The

core of the tablet remains essentially dry at this stage. In the case of a highly soluble drug, this phenomenon may lead to an initial burst release due to the presence of the drug on the surface of the matrix tablet. The gel layer (rubbery state) grows with time as more water permeates into the core of the matrix, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, thereby leading to disentanglement and erosion of the surface of the matrix. Water continues to penetrate towards the core of the tablet, through the gel layer, until it has been completely eroded. Soluble drugs can be released by a combination of diffusion and erosion mechanisms whereas erosion is the predominant mechanism for insoluble drugs. For successful extended release of drugs, it is essential that polymer hydration and surface gel layer formation are quick so as to prevent immediate tablet disintegration and premature drug release. For this reason, polymers for hydrophilic matrices are usually supplied in small particle size to ensure rapid hydration and consistent formation of the gel layer on the surface of the tablet. A large number of mathematical models have been developed to describe drug release profiles from matrices. The simple and more widely used model is the one derived by Korsmeyer et al. and is as follows:

$$M_t / M_\alpha = k\, t\, n \quad \text{---------- (1)}$$

where M_t / M_a is the fraction of drug release, k is the diffusion rate constant, t is the release time and n is the release exponent indicative of the mechanism of drug release. The equation was modified by Ford et al. to account for any lag time or initial burst release of the drug

$$Mt / Ma = k\,(t - 1)\,n \text{---------- (2)}$$

Where l = lag time. It is clear from both equations that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). Here, the polymer relaxation and erosion are the rate-controlling steps. When n = 0.5, Fickian diffusion is the rate-controlling step (case I transport). Values of n between 0.5 and 1 indicate the contribution of both the diffusion process as well as polymer relaxation in controlling the release kinetics (non-Fickian, anomalous or first-order release). It should be noted that the two extreme values of n = 0.5 and 1 are only valid for slab geometry. For cylindrical tablets, these values range from $0.45 < n < 0.89$ for Fickian, anomalous or case II transport respectively.

1.4. Angina pectoris

Angina pectoris, commonly known as angina, is severe chest pain due to ischemia (a lack of blood, hence a lack of oxygen supply) of the heart muscle, generally due to obstruction or spasm of the coronary arteries. Coronary artery disease, the main cause of angina, is due to atherosclerosis of the cardiac arteries. The term derives from the Latin angina ("infection of the throat") from the Greek ἀγχόνη ankhone ("strangling"), and the Latin pectus ("chest"), and can therefore be translated as "a strangling feeling in the chest".

Types of angina pectoris

Stable angina

Stable angina is a repeating pattern of chest pain which has not changed in character, frequency, intensity or duration for several weeks. The level of activity or

stress that provokes angina is predictable and the pattern changes slowly. Stable angina is the most common form and it appears gradually. These patients have an increased risk of a heart attack, but an episode of stable angina does not indicate that a heart attack is about to happen.

Pathology

Severe arteriosclerotic affliction of larger coronary arteries. Which run epicardially and send perforating branches to supply the deeper tissue. The coronary obstructions are fixed, blood flow fails to increase during increased demand despite local factors mediated dilatation of resistance vessels and ischemic pain is felt. Thus a form of acutely developing and rapidly reversible left ventricular failure results which is relieved by taking rest and reducing the myocardial work load (KD. Tripathi, 2008).

Unstable angina

Unstable angina is chest pain that is variable, either increasing in frequency or intensity and with irregular timing or duration. Unlike stable angina, unstable angina does not appear gradually, it first appears as a severe episode (KD. Tripathi, 2008). An established stable angina might change suddenly or be provoked by less stress than in the past or an episode might suddenly occur while at rest. If the pattern of an episode changes, for example if a previous episode was only brought on during physical exertion, but an episode suddenly occurred at rest it is likely to be unstable angina.

Prinzmetal's angina

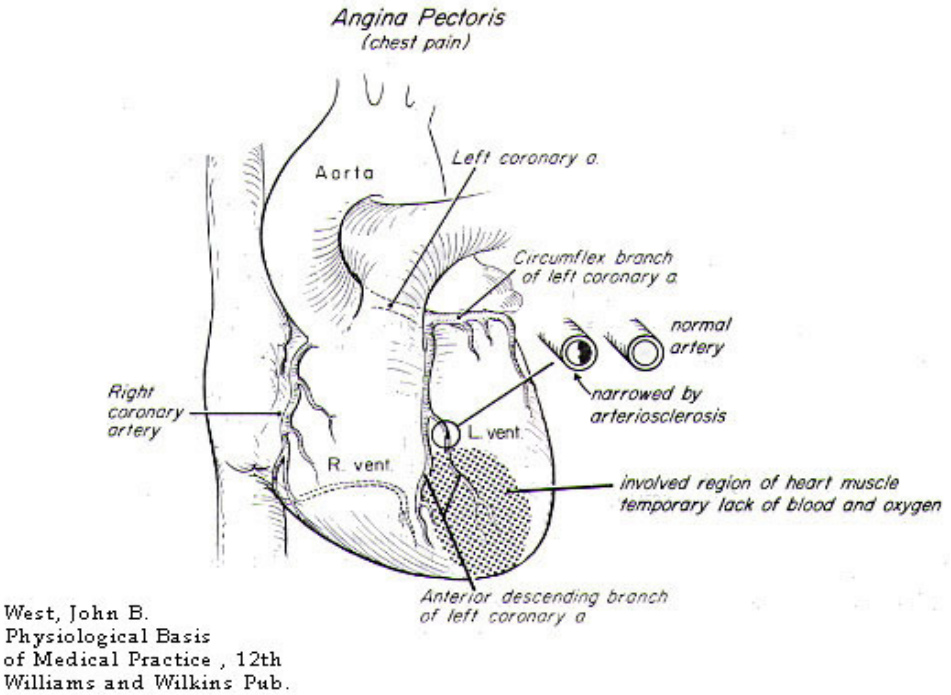
Prinzmetal’s or variant angina is caused by a vasospasm, a spasm that narrows the coronary artery and lessens the blood flow to the heart. Prinzmetal's

Angina usually occurs in arteries already narrowed by atherosclerosis; in fact most people with it have severe coronary.

Mechanism of relief of angina

The dilator effect on larger coronary vessels is the principal action of nitrates benefiting variant angina by counter acting coronary spasm. In classical angina undoubtedly the primary effect is to reduce cardiac work by action on peripheral vasculature, though increased blood supply to ischemic area may contribute. Exercise tolerance of angina patients is increased because the same amount of exercise causes lesser augmentation of cardiac work.

Figure 4: Dysfunction of heart due to Angina pectoris



What causes angina?

The most common cause of angina is coronary artery disease. A less common cause of angina is spasm of the coronary arteries.

Coronary artery disease

Coronary arteries supply oxygenated blood to the heart muscle. Coronary artery disease develops as cholesterol is deposited in the artery wall, causing the formation of a hard, thick substance called cholesterol plaque. The accumulation of cholesterol plaque over time causes narrowing of the coronary arteries, a process called arteriosclerosis. Arteriosclerosis can be accelerated bysmoking, high blood pressure, elevated cholesterol, and diabetes. When coronary arteries become narrowed by more than 50% to 70%, they can no longer meet the increased blood oxygen demand by the heart muscle during exercise or stress. Lack of oxygen to the heart muscle causes chest pain (angina).

Coronary artery spasm

The walls of the arteries are surrounded by muscle fibers. Rapid contraction of these muscle fibers causes a sudden narrowing (spasm) of the arteries. A spasm of the coronary arteries reduces blood to the heart muscle and causes angina. Angina as a result of a coronary artery spasm is called "variant" angina or Prinzmetal angina. Prinzmetal angina typically occurs at rest, usually in the early morning hours. Spasms can occur in normal coronary arteries as well as in those narrowed by arteriosclerosis. Coronary artery spasm can also be caused by use/abuse of cocaine. The spasm of the artery wall caused by cocaine can be so significant that it can actually cause a heart attack.

Treatment of angina pectoris:

The main goals of treatment in angina pectoris are relief of symptoms, slowing progression of the disease, and reduction of future events, especially heart attacks and of course death. An aspirin (75 mg to 100 mg) per day has been shown to be beneficial for all patients with stable angina that have no problems with its use. Beta blocker (eg. Carvedilol, Propranolol and Atenolol etc are few examples) have a large body of evidence in morbidity and mortality benefits (fewer symptoms and disability and live longer) and short-acting nitroglycerin medications are used for symptomatic relief of angina. Calcium channel blockers (such as Nifedipine and Amlodipine), Isosorbide mononitrate and Nicorandil are vasodilators commonly used in chronic stable angina. A new therapeutic class, called If inhibitor, has recently been made available: Ivabradine provides pure heart rate reduction,.[1] Leading to major anti-ischemic and antianginal efficacy. ACE inhibitors are also vasodilators with both symptomati prognostic benefit and lastly, statins are the most frequently used lipid/cholesterol modifiers which probably also stabilise existing atheromatous plaqu

Nitrates

Short Acting: Glyceryl trinitrate (GTN, Nitroglycerine)

Long Acting: Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate, Erythrityl tetranitrate, Penta erythritol tetranitrate.

ß-Blockers

Propranolol, Metoprolol, Atenolol and others.

Calcium Channel Blockers

Phenyl Alkylamine: Verapamil

Benzothiazepine: Diltiazem

Dihydropyridines: Nifedipine, Felodipine, Amlodipine, Nitrendipine,

Nimodipine, Lacidipine.

Potassium Channel Opener

Nicorandil, Penacidil and Dizoxide

Others

Dipyridamole, Trimetazidine, Oxyphedrine.

2. LITERATURE REVIEW

Anil Kumar. SN et al., (2010) the aim of the present study is to develop colon targeted drug delivery systems for Trimetazidine Hcl using sodium alginate as a carrier. In this study, investigation of an oral colon specific, pulsatile device to achieve time or site specific release of Trimetazidine, based on chronopharmaceutical considerations. The basic design consists of an insoluble hard gelatin capsule body, filled with sodium alginate microsphere of trimetazidine and sealed with a hydrogel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. Different concentration of the hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. FTIR study confirmed that there was no interaction between drug and polymer, the shape of microsphere was foundto be spherical by SEM studies. In vitro release studies of pulsatile device revealed that, increasing the hydrophilic polymer content resulted in delayed release of trimetazidine from microspheres.

Abhijit N. Merekar et al., (2010) monolithic matrix tablets of *Trimetazidine Dihydrochloride* were formulated as modified release tablet employing hydroxy propyl methyl cellulose polymer, and the modified release behavior of fabricated tablets was investigated. Modified released matrix tablets contain 35.7 mg *Trimetazidine Dihydrochloride* were developed using different drug polymer concentration of H. P. M. C. Tablets were prepared by wet granulation using I.P.A. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release.. All tablets but one

exhibited gradual and near completion modified release for *Trimetazidine Dihydrochloride*, and 98.5 to 101.5% released at the end of 8 h. An increase in release kineticsof the drug was observed on decreasing polymer concentration.

Basu S.K et al., (2010) microspheres of Trimetazidine Hydrochloride (TZ) were prepared by coacervation method without the use of chemical cross–linking agents such as glutaraldehyde to avoid the toxic reactions and other undesirable effects of the chemical cross-linking agents. Alternatively, ionotropic gelation was employed by using sodium-tripolyphosphate (Na-TPP) as cross linking agent. Chitosan was used as polymer. All the prepared microspheres were subjected in-vitro drug release characteristics and release kinetics. TLC and FTIR studies indicated no drug-polymer incompatibility. As the drug to polymer ratio was increased, the mean particle size (MPS) of TZ microspheres was also increased. A maximum of 80% of drug entrapment efficiency was obtained by the method employed. All the MS showed zero order release kinetics followed by a Fickian diffusion mechanism. From the above data it was concluded that it may be possible to design a controlled drug delivery system for the prolonged release of TZ, improving therapy by possible reduction of time intervals between administrations.

Raj Kumar et al., (2010) the purpose of the present study was to formulate the oral controlled release Trimtazidine di hydrochloride tablets by using Polysaccharide B-1459 (14-38%) as rate controlling polymer. The tablets were prepared by direct compression method and coated by the film coating polymers. The powder mixtures were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index, shows satisfactory results. All the ingredients were lubricated and compressed

using 8mm circular shaped deep concave punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, thickness, friability, hardness and In-vitro dissolution studies. The in vitro release study of matrix tablets were carried out in 0.1N Hydrochloric acid with pH 1.2 for 10 hours. The prepared matrix tablets were shown 99.00%, 100.00%, 104.00%, 92.00% and 100.00% release over a period of 10 hours. It was observed that the amount of polymer influences the drug release. In vitro release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration.

Punit B. Parejiya et al., (2010) formulated a Sustained release Aceclofenac matrix tablets constituting Kollidon SR (Polyvinyl acetatepovidone based matrix retarding polymer) were developed for manifesting desirable release profile. Matrix tablets were prepared by direct compression of Kollidon SR varying proportion with fixed percentage of aceclofenac. Tablets containing 50 % Kollidon SR demonstrated a rapid rate of drug release with an initial burst effect. Incorporation of more Kollidon SR in the tablet prolonged drug release with subsequent minimization of burst effect as confirmed by mean dissolution time, dissolution efficiency, f2 and drug release kinetic data. The formulation showed close resemblance to commercial product Senafen. The results were explored and explained by the difference of physico-chemical property and micromeritic characteristics. Insignificant effect of various factors e.g. pH, ionic strength, paddle speed was found on drug release. The formulation followed Korsmeyer and peppas kinetic of drug release. Stability study data indicated stable character after short term stability study.

Bhupendra et al., (2010) has revealed that the hydrophilic polymer (HPMC K200M) and hydrophobic polymer (EC, Eudragit RSPO) based Nicorandil matrix SR tablet which can release drug up to time of 24hrs. Hydrophilic and Hydrophobic polymer combination gives good result than alone hydrophilic or hydrophobic polymer is used.

Gothi G.D et al., (2010*)* in the present investigation an attempt was made to reduce the frequency of dose administration, to prevent nocturnal heart attack and to improve the patient compliance by developing extended release (ER) matrix tablet of metoprolol succinate. The effect of concentration of hydrophilic (hydroxypropyl methylcellulose [HPMC K 100 M], xanthan gum) on the release rate of metoprolol succinate was studied. Hydrophilic matrix tablets were prepared by wet granulation technique and evaluated for various parameters like, weight variation, content uniformity, in-vitro dissolution. and *in vitro* dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. The drug release kinetics was found to be governing by the type of the amount of the polymer in the matrix system. The higher polymeric content in the matrix decrease the release rate of the drug. At lower polymeric level, the rate and extent of drug release were evaluated. All formulation showed compliance with pharmacopoeial standards. The studies indicated that the drug release can be modulated by varying the concentration of the polymer. Among the ten formulations**,** F9 best matched formulation with respect to market product. Optimized formulation was found stable during accelerated stability study for 3 months at 400C/75% RH.

Y Haung et al., (2009) developed and optimized the propranolol once-daily substained release formulations containing HPMC, Microcrystalline cellulose (MCC) and lactose. In vitro studies, the response surface methodology and polynomial equation were used to search for the optimal formulation with specific release rate at different time intervals. The constrained mixture experimental design was used to prepare systematic model formulations, which were composed of three formulation variables: the content of HPMC (X(1)) MCC (X(2)) and lactose (X(3)). The drug release percent at 1.5, 4, 8, 14 and 24 h were the target responses and were restricted to 15-30, 35-55, 55-75, 75-90 and 90-110%, respectively.

M. Ganesh, et al., (2009) was developed a new validated spectrophotometric method for determination of class III drug in Formulation and comparison with UV method.

A.Hamid et al., (2006) formulated and Evaluated of Once-Daily tablets of Cefpodoxime using hydroxypropyl methylcellulose. Tablets were prepared by direct compression. In vitro drug release was evaluated using USP Apparatus-II. It was found that 16.86% of the drug was released during the first hour. During the initial 9 hours, ~50% of the drug was released. After 9 hours, the release rate increased slightly, until the 21st hour, and then release slowed but continued until the 24-hour mark. Hence, the formulation can be considered as a once-daily sustained-release tablet of Cefpodoxime Proxetil.

A Kuksal et al., (2006) prepared and characterized sustained-release matrix tablets of zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. Release kinetics was evaluated by using (USP)-22 type I dissolution apparatus. The in vitro and in vivo newly formulated sustained--release zidovudine tablets were compared with conventional marketed. The in-vitro drug release study revealed that either Eudragit. Preparation was able to sustain the drug release only for 6 hours (94.3% ± 4.5% release). Combining Eudragit with ethyl cellulose sustained the drug release for 12 hours (88.1% ± 4.1% release). Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release**.**

M. Harris shoaib et al., (2006) have been developed once-daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

Gabriele Fragasso et al., (2006) reported that the long-term addition of Class III drug improves functional class and left ventricular function in patients with heart failure (HF).

Sung-Up Choi et al., (2003) designed and evaluate a directly compressible hydrophilic poly(ethylene oxide) (PEO) matrix for the oral sustained delivery of dihydrocodeine bitartrate (DHCT). A direct compression method was used to prepare PEO matrices, and the amount of PEO in the matrices was varied to optimize in vitro DHCT release profiles. From the data obtained in this research, hydrophilic PEO matrices were found to be a novel sustained-release carrier for the oral delivery.

David A. Fairman et al., (2003) reported the class III drug acts as an effective antianginal clinical agent by modulating cardiac energy metabolism. It selectively inhibits long-chain 3-ketoacyl CoA thiolase (LC 3-KAT), there by reducing fatty acid oxidation resulting in clinical benefit.

YSR Krishnaiah et al., (2002) formulated "Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble class III drug" using guar gum as a carrier. Matrix tablet granules containing 30%, 40% or 50% of guar gum were prepared by the wet granulation technique using starch paste as a binder. The three-layer guar gum matrix tablet estimated using a HPLC method, provided the required release rate compare with the theoretical release rate for guar gum formulations meant for twice daily administration. The results indicated that guar gum, in the form of three-layer

matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs.

Gidwani, Prashant Kumar et al., (2002) designed sustained release matrix pharmaceutical compositions containing 60mg of class III drug constituting 8 to 50% by weight of the composition and hydrophobic polymers as a retardant by hot melt granulation at a temperature of 40°C to 120°C, which release drug in a sustained and reproducible manner over 24 hour. The Diluent comprises 10 to 70% by weight of the composition such as calcium carbonate. Binder comprises 2 to 10% consisting of gelatin and gum acacia. Glidant comprises 0.5 to 1.5% by weight of the composition consisting of colloidal silicone dioxide. Lubricant comprises 0.5 to 1.0% by weight of the composition selected from magnesium stearate. The tablets were film coated with 0.5 to 4.0% by weight of the tablet using cellulose derivatives. The dissolution was carried out in gastric simulated fluid pH 1.2 for the first hour and then in phosphate buffer pH 6.8 USP.

Purushottam S et al., (2002). was developed sustained release matrix compositions containing 60 mg of Class III drug and hydrocolloid forming materials such as HPMC, HPC, Povidone, SCMC, Sodium alginate, Polyvinyl alcohol, Xanthan gum. Hydrophobic polymers as a retardant which release drug in a sustained and reproducible manner over a prolonged period of time to achieve the sustained effect of drug over a 24 hour period after oral administration.

. **Tulsidutt et al., (2002)** designed sustained release matrix pharmaceutical compositions characterized by the absence of cellulose and/or their derivatives as release

modifying agent containing, class III drug constituting 8 to 50% by weight of total composition formulated either water soluble material such as Polyethylene oxide, Sodium alginate, Calcium alginate and Xanthan Gum and water insoluble material such as stearic acid and polyvinyl acetate, or water swellable material such as guar gum, alginic acid.

Gilbert Regnier et al., (1994) reported that the Class III drug is useful for the treatment of ischeamic pathologies and peripheral vascular pathology.

3. AIM AND PLAN OF WORK

3.1. Aim

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for Extended release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products.

The primary objective of the extended release (Matrix) drug delivery system is to ensure safety and to improve efficacy of drug as well as patient compliance. The present invention provides a novel sustained release composition comprising Trimetazidine Dihydrochloride**.** The objective of the present study was to formulate and evaluate once daily extended release matrix tablets of Trimetazidine Dihydrochloride using hydrophilic polymers Hydroxypropylmethylcellulose, Polyox, and natural polymer Xanthan gum.

Trimetazidine has a half life 6 hrs and usual oral dosage regimen 0.5 mg and 60 mg daily. To reduce the frequency of administration and to improve patient compliance, a once-daily extended release formulation of Trimetazidine is desirable. The most commonly used method of modulating the drug release is to include it in a matrix system. Hydrophilic polymer matrix systems were widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug-release profile, they are cost effective and they have broad US Food and Drug Administration acceptance.

Hence, in present work, an attempt has been made to develop once daily sustained release matrix tablets of Trimetazidine using putative hydrophilic matrix

materials. The drug release for extended duration using a hydrophilic matrix system is restricted because of rapid diffusion of dissolved drug through the hydrophilic gel network. For such circumstances, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained release dosage forms.

3.2. Plan of work

1) Literature Survey.
2) Innovator characterization.
    a) Physical evaluation.
    b) Chemical evaluation.
3) Preformulation studies.
    a) Compatibility studies with excipients.
    b) Excipients selection.
    c) API physical and chemical evaluation.
4) Formulation Development.
    a) Process evaluation.
    b) Formula evaluation.
    c) Process optimization.
5) Formulation evaluation.
    a) Physical evaluation.
    b) Chemical evaluation.
6) Stability studies.

4. MATERIALS AND METHODS

4.1. Materials used

The materials employed in the formulation and evaluation and the corresponding manufacturers were listed in the following table.

Table 1: List of materials used in formulation development.

S. No	Ingredient	Manufacturer
1	*Trimetazidine dihydrochloride*	Nivedita chemicals- Mumbai
2	Anhydrous calcium hydrogen phosphateBP/Ph.Eur	Innophos inc- United States
3	Polyethylene oxide (Polyox WSR 301 LEO) NF	Dow chemical's- Tamil Nadu
4	HPMC K 200 M BP/USP/Ph.Eur	Dow chemical's- Tamil Nadu
5	Xanthan gum FF BP/Ph.Eur	Lucid colloids ltd -Mumbai
6	Povidone BP/Ph.Eur (K90F)	BASF –Germany
7	Colloidal Anhydrous Silica	Deggusa
8	Magnesium stearate BP/Ph.Eur.	Vijlak Pharma Ltd-Hyderabad

4.2. Equipment used

Table 2: Equipments used

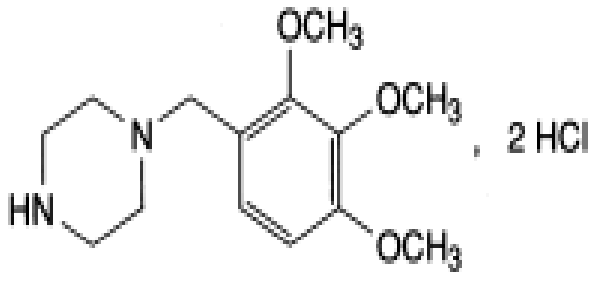
S. No	Name of equipment	Manufacturer
1	Digital Weighing balance	Essae digi
2	Vibratory Sifter	Ganson / Anchor
3	Octagonal Blender	Ganson / Bectochem
4	Tablet Compression machine	Cadmach Machinery Pvt. Ltd
5	Vernier callipers	Mitatoyo
6	Friability apparatus	Electrolab
7	Hardness tester	Varian
8	Six station dissolution tesapparatus	Electro Lab
9	UV-Visible Spectrophotometer	Shimadzu
10	Blister Packing Machine	Ezee Blister

4.3. Drug and excipient profile

4.3.1. Drug Profile (European Pharmacopoeia, 2005)

Trimetazidine Dihydrochloride

Figure 5: Structure of *Trimetazidine dihydrochloride*



Category: Antiangina.

Empirical Formula: $C_{14}H_{22}N_2O_3.2HCl$.

Chemical name: (2, 3, 4-Trimethoxybenzyl) piperazine dihydrochloride

Trimetazidine Dihydrochloride contains not less than 98.5 percent and not more than 101.5 per cent, calculated on the dried basis.

Molecular Weight: 339.26 g/mol.

Appearance, odor and Color: White crystalline powder.o

Melting Point: Between 225° and 227° **.**

Identification: Identified by IR Spectrophotometer by KBr disc method.

pKa: pKa values 4.32 and 8.95 .

Solubility: Soluble in water, sparingly soluble in ethanol & practically insoluble in ether.

Assay

Dissolve 0.12g in 50.0 ml of water. Add 1 ml of nitric acid and titrate with 0.1M silver nitrate, determining the end point potentiometrically (2.4.25).Carry out a blank titration. 1 ml of 0.1N silver nitrate is equivalent to 0.011696 g of $C_{14}H_{24}Cl_2N_2O_3$.

Pharmacokinetic data.

Bioavailability: 87%.

Metabolism: Myocardial, free fatty acid.

Half life: 6 hrs.

Protein binding: 16%.

Excretion: Renal.

Pharmacodynamic properties

Class III drug is a unique anti-ischemic drug, which protects the myocardial cell from the harmful effects of ischemia (M. Marzilli et al., 2001).

Mechanism of action

The mode of action is drug is different from beta-blockers, calcium channel determinants of myocardial oxygen supply-demand balance; Class III drug prevents the damage to the myocardial cell during an ischemic pisode. Drug inhibits fatty acid oxidation secondary to an inhibition of long-chain 3-ketoacyl CoA thiolase (KAT), resulting in an increase in glucose oxidation. This results in switching energy substrate preference from fatty acid oxidation to the more efficient glucose oxidation which explains the anti anginal properties. Drug prevents intracellular metabolic changes such as depletion of adenosine triphosphate (ATP) and phosphocreatinine accumulation of protons, and toxic free radical generation which result from ischaemia and reperfusion in the myocardium.

Clinical Pharmacology

Therapeutic Uses

Trimetazidine dihydrochloride is indicated in the treatment of ischemic heart disease (angina pectoris, sequelae of infarction).

Adverse reaction

The most commonly encountered side effects are gastric discomfort, nausea, headache and vertigo. However, the side effects are mild and non-specific.

Drug interaction

No drug interactions have been reported. In particular, no interactions have been reported with beta-blockers, calcium antagonists, nitrates, heparin and digitalis preparation.

Precautions

Renal and hepatic impairment

No dosage adjustments are required in patients with impaired renal and hepatic function.

Pregnancy

There is insufficient evidence to recommend the use of Class III drug in pregnancy.

Lactation

There is no information on the secretion of class III drug into breast milk. However, breast-feeding should be discontinued if the use of class III drug is considered essential. In general, use of this medication by nursing mothers is not recommended.

Pediatric use

There is no data available for the use of class III drug in children.

Dosage

Adults: 60mg 1 time a day.

4.3.2. Polymer profile (Raymond C Rowe, 1995).

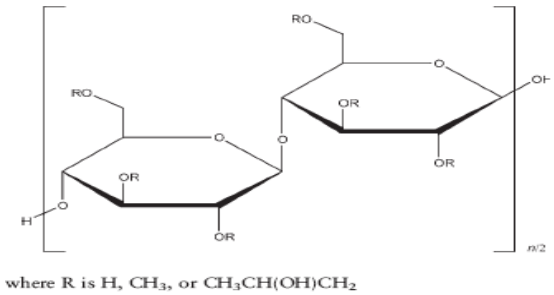
Hydroxy propyl methylcellulose

Synonyms: Benecel MHPC, methocel, metolose, Pharmacoat, spectracel, tylopur.

Chemical name: Cellulose, 2-Hydroxypropyl methyl ether.

Empirical formula: HPMC is a partly o-methylated and o- (2-hydroxypropylated).

Figure 6: Structure of hydroxy propyl methyl cellulose



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Molecular weight: Approx. 10000-1500000

Functional category

Bioadhesive, Emulsifying agent, release modifying agent, sustained release agent, suspending agent, tablet binder, viscosity-increasing agent, film forming agent.

Description: Odorless, tasteless, white or creamy white fibrous or granular powder.

Aqueous viscosity: HPMC K 15 - 15000 mPas.

Solubility

Soluble in cold water, insoluble in alcohol, ether and chloroform but soluble in a mixture of methylene chloride and methanol.

Stability and storage condition

Stable in dry condition from pH 3.0 to 11.0 although it is hygroscopic in nature. Should be store in well closed container, in a cool and dry place.

Incompatibilities

Incompatible with some oxidizing agents. Since it is nonionic, hydroxy methylcellulose will not complex with metallic effect.

Safety

It's generally regarded as a nontoxic and non-irritant material although excessive oral consumption may have a laxative effect.

Application

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. It is also used in extended release matrix.

Polyethylene oxide

Synonyms: Polyox; polyoxirane, polyoxyethylene.

Chemical name and cas registry number: Polyethylene oxide [25322-68-3].

Molecular weight: 4 000 000.

Structural formula

The USPNF 23 describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula (CH2CH2O)n, where n represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide.

Functional category: Mucoadhesive, tablet binder, thickening agent.

Applications in pharmaceutical formulation or technology

Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach.

Description: White to off-white, free-flowing powder, slight ammonical odor.

Typical properties

Angle of repose : 348

Density (true) : 1.3 g/cm^3

Melting point : 65–70° C

Moisture content : <1%

Solubility

Polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.(2) Viscosity (dynamic).

Stability and storage conditions

Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

Incompatibilities

Polyethylene oxide is incompatible with strong oxidizing agents.

Safety

Animal studies suggest that polyethylene oxide has a low level of toxicity regardless of the route of administration. It is poorly absorbed from the gastrointestinal tract but appears to be completely and rapidly eliminated. The resins are neither skin irritants nor sensitizers, and they do not cause eye irritation.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Regulatory Status

Included in the FDA Inactive Ingredients Guide (sustained release tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Xanthan gum

Synonyms

Corn sugar gum, E415, Keltrol, polysaccharide B-1459, Rhodigel, Vanzan NF, Xantural.

Chemical name: Xanthan gum.

Cas registry number: [11138-66-2].

Molecular formula: (C35H49O29) n .

Description

Xanthan gum occurs as a cream- or white-colored, odourless, free-flowing, fine powder.

Solubility

Practically insoluble in ethanol and ether;, soluble in cold or warm water.

Viscosity

1200–1600 mPas (1200–1600 cP) for a 1% w/v aqueous solution at 258°C.

Structural formula

Each xanthan gum repeat unit contains five sugar residues: two glucose, two mannose, and one glucuronic acid. The polymer backbone consists of four b-D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydroglucose units distinguish xanthan from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the mannose nearest the main chain carries a single group at C-6. The resulting stiff polymer chain may exist in solution as a single, double, or triple helix that interacts with other xanthan gum molecules to form complex, loosely bound networks.

Functional category

Gelling agent, stabilizing agent, suspending agent, sustained-release agent, viscosity-increasing agent.

Application

Xanthan gum is used to prepare sustained-release matrix. Xanthan gum has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation.

Safety

The estimated acceptable daily intake for Xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.

Stability and storage condition

Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–608°C.

Incompatibilities

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral solutions, suspensions, and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

4.3.3. Excipient profile (Raymond C Rowe, 1995).

Povidone.

Synonyms

Kollidon, Plasdone; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical name: 1-Ethenyl-2-pyrrolidinone homopolymer.

Molecular formula: (C6H9NO) n.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odourless, hygroscopic powder.

Melting point: Softens at 150 ^{0}C.

Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

Stability and storage conditions

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.

Safety

When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization.

Application

In tableting, povidone solutions are used as binders in wet granulation processes.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Regulatory status

Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (IM and IV injections, ophthalmic preparations, oral capsules, drops, granules, suspensions, and tablets, sublingual tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the canadian list of acceptable nonmedicinal ingredients.

Anhydrous calcium hydrogen phosphate

Synonyms

Calcium ortho phosphate, Dicalcium ortho phosphate, phosphoric acid calcium salt (1: 1).

Chemical Name: Dibasic calcium phosphate.

Description

Anhydrous dibasic calcium phosphate is a white, odorless, tasteless powder or crystalline solid.

Empirical formula: $CaHPO_4$

Solubility: Practically insoluble in ether, ethanol, and water; soluble in dilute acids.

Functional categories: Tablet and capsule diluent.

Angle of repose: 28.3°.

Density (bulk): 0.78 g/cm^3.

Density (tapped): 0.82 g/cm^3 .

Melting point: Decomposes at 425°C to form calcium pyrophosphate.

Applications

Anhydrous dibasic calcium phosphate is used both as an excipient and as a source of calcium in nutritional supplements. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material.

Incompatibilities

Dibasic calcium phosphate should not be used to formulate tetracycline antibiotics.

Stability and storage conditions

Dibasic calcium phosphate anhydrous is a nonhygroscopic, relatively stable material. Under conditions of high humidity it does not hydrate to form the dihydrate. The bulk material should be stored in a well-closed container in a dry place.

Safety

Dibasic calcium phosphate anhydrous is widely used in oral pharmaceutical products, food products, and toothpastes and is generally regarded as a relatively nontoxic and nonirritant material.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. The fine-milled grades can generate nuisance dusts and the use of a respirator or dust mask may be necessary.

Regulatory status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Colloidal anhydrous silica

Synonyms

Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, Colloidal silica, Fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, Wacker HDK.

Chemical name: Silica.

Description

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

Structural formula: SiO_2.

Solubility

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Functional categories

Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer and viscosity-increasing agent.

pH: 3.5 – 4.4 (4% w/v aqueous dispersion).

Density (bulk): 0.029 – 0.042 g/cm^3 .

Applications

Used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

Aerosols	-	0.5–2.0 %
Emulsion stabilizer	-	1.0–5.0 %
Glidant	-	0.1–0.5 %
Suspending and thickening agent	-	2.0–10.0 %

Incompatibilities

Incompatible with diethylstilbestrol preparations.

Stability and storage

It is hygroscopic. Should be stored in a well-closed container. At pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely.

Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. In the absence of suitable containment facilities, a dust mask should be worn when handling small quantities of material. For larger quantities, a dust respirator is recommended. Inhalation of colloidal silicon dioxide dust may cause irritation to the respiratory tract but it is not associated with fibrosis of the lungs (silicosis), which can occur upon exposure to crystalline silica.

Regulatory acceptance

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets, transdermal and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Magnesium stearate

Synonyms

Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate.

Chemical name: Octadecanoic acid magnesium salt.

Description

If is a fine, white, precipitated of milled, impalpable powder of low bulk density, having a faint odor of stearic acid & a characteristic taste.

Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$.

Solubility

It is insoluble in water, ethanol & ether, slightly soluble in warm benzene & warm ethanol.

Functional categories: Table & capsule lubricant.

Melting point: 117- 150°C.

Density (bulk): 0.159gm/cm^3.

Density (tapped): 0.286gm/cm^3.

Stability and storage conditions

Should be stored in well-closed container in a cool, dry place. It is stable compound.

Incompatibilities

Incompatible with strong oxidizing agents, strong acids, alkalis & iron salts. It cannot be used in products containing aspirin, some vitamins, & most alkaloidal salts.

Safety

It is nontoxic. However, oral consumption of large quantity may result in some laxative effect or mucosal irritation.

Applications

Used in cosmetics, food & pharmaceutical formulations and as a lubricant in capsule & table at concentration between 0.25-5.0%.

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well ventilated environment; a respirator is recommended.

Regulatory acceptance

GRAS listed. Accepted as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (oral capsules, powders, and tablets, buccal and vaginal

tablets, topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian list of acceptable non-medicinal ingredients.

4.4. Preformulation studies

Before formulation of drug substances into a dosage form, it is essential that calibration graph,drug & polymer should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

Construction of calibration curve

An accurately weighed 100 mg of *Trimetazidine* was dissolved in phosphate buffer of pH 6.8 separately and make up the volume up to 100 ml in a volumetric flask (Stock Solution: I, 1000 µg/ml) . From this 10 ml of solution were pipette out and make up the volume up to 100 ml (Stock Solution: II, 100 µg/ml). Then the aliquots were prepared, whose concentration ranging from 0 to 33 µg/ml and the absorbance was measured at 231 nm (Abhijit. N et al., 2010) by using UV Spectrophotometer (Shimadzu, Model No: 2450) against the blank.

Drug-excipient compatibility studies by FT-IR

One of the requirements for the selection of suitable excipients or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction of *Trimetazidine dihydrochloride* drug with Polyethylene oxide WSR 301NF, HPMC K200M, Xanthan gum and placebo used for the study.

Procedure

Weighed amount of drug (1 mg) was mixed with 99 mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and compressed under 7-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned in IR spectrophotometer.

Drug excipient compatibility studies by force degradation studies

The Binary mixtures of drug and excipients (1:1) were prepared, and packed in both closed vials and kept in both long term and accelerated environmental conditions **(25^{0}C/60% RH and 40^{0}C/75% RH)** for 1 month. At the end of 1 month period all the samples were observed physically.

4.5. Preparation of a sustained release tablets

Design of formula and composition

The design of tablets involved various compromises on the part of the formulator, to produce desired product properties. It involves the correct selection and balance of excipients materials for active ingredients to achieve the desired response.

Based on primary information collected from market samples and previous experience with the manufacturing of various products, the following tentative product specifications were proposed before starting the formulation trials.

Type of sustained release system proposed

Matrix with SR controlling tablets.

Justification for the design of the formula composition

In addition to the active, *Trimetazidine dihydrochloride* 60 mg SR tablets contained a number of inert materials as diluents, binders, and lubricants, compression and release characteristics to the formulation. The justification for the inclusion of these functional additives is briefly described below.

Diluents

They are inert materials added to increase the bulk in order to make the tablet with a desired particle size for compression.

Dicalcium phosphate anhydrous was used in the present development as directly compressible materials and improves the flow properties of the blend.

Binders

Materials used to impart cohesive quality to the powdered materials are referred to as binders. They impart cohesiveness to the tablet formulation which insures the tablet remaining intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size. In the present study povidone K90F was selected as binder.

Lubricants

They prevent the adhesion of the tablet material to the surface of the dies and punches reduces inter-particle friction, facilitate the ejection of the tablet from the die cavity and improve the rate of flow of the tablet granulation.

In the present study, Magnesium stearate was used as lubricant. It is hydrophobic in nature. It was a proper choice as the tablet did not show any tendency to stick to the side of the die. The tablets were found to be satisfactory and the dissolution profile of the drug substance was satisfactory with the use of Magnesium stearate.

Dispensing of materials

All the solid raw materials are dispensed, packed in individual cleaned Poly ethylene bags and labeled.

4.6. Formulation

Table 3: Composition of SR tablets of *Trimetazidine dihydrochloride.*

S. No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
1	Trimetazidine diHcl	60	60	60	60	60	60	60	60
2	Dicalcium phosphate	235	175	115	55	235	175	115	55
3	Povidone K90F	10	10	10	10	10	10	10	10
4	Xanthan gum	120	120	120	120	120	120	120	120
5	HPMC K200M	__	----	----	----	60	120	180	240
6	Polyox WSR 303	60	120	180	240	__	----	----	---
7	Colloidal anhydroussilica	10	10	10	10	10	10	10	10
8	Magnesium stearate	5	5	5	5	5	5	5	5
9	One tablet weight	500	500	500	500	500	500	500	500

Sifting

Separately sift *Trimetazidine dihydrochloride*, Colloidal anhydrous silica, Polyethylene oxide [Sentry Polyox WSR 303 LEO], Povidone K90 , Hydroxypropyl methyl cellulose K 200M, Xanthan gum and anhydrous calcium hydrogen phosphate through #30 mesh and Magnesium stearate through #60 mesh. Collect all the above sifted materials individually into a double lined polyethylene bag.

Mixing

Load sifted *Trimetazidine dihydrochloride*, anhydrous calcium hydrogen phosphate, Colloidal anhydrous silica and Povidone K 90 into octagonal blender and mix for 10 minutes.

Pre-Lubrication and Lubrication

To the above blend, add Xanthan gum/ polyox / HPMC and pre-lubricate for 10 minutes. Lubricate the above blend with Magnesium stearate in the octagonal blender for 5 minutes.

4.7. Evaluation of Blend

Angle of repose:

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

$$\theta = \tan^{-1} (h/r)$$

Where,

h = height

r = radius

θ = angle of repose

Procedure

An accurately weighed sample was taken. A funnel was fixed in the stand in such a way that the tip of the funnel was at the height of 6 cm from the surface. The sample was passed through the funnel slowly to form a heap. The height and the circumference of the powder heap formed were measured. The radius was measured and the angle of repose was determined using the above formula. This was repeated three times for a sample.

Determination of bulk density and tapped density

A quantity of 10 gm of the powder (W) from each formula was introduced into a 50 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted (Shah D et al., 1997, Aulton ME, 1988).

The bulk density and tapped density were calculated using the following formulas

$$\text{Bulk density} = W / V_O$$

$$\text{Tapped density} = W / V_f$$

Where,

W = weight of the powder.

V_O = initial volume.

V_f = final volume.

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density (Rajiv Garg, 2002).

Hausner's Ratio = Tapped density/Bulk density

Table 4: Limits of hausner's ratio as per USP

S. No	Hausner's ratio	Property
1.	Less than 1.25	Free flow
2.	1.25 to 1.5	Glidant to be added
3.	More than 1.5	Poor flow

Compressibility index (Carr's indices)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, less the compressibility of a material, it is more flowable. A material having values of less than 20 to 30% is defined as the free flowing material (Aulton ME, 1988).

$$C_I = 100\ (V_O - V_f)/V_0$$

Table 5: Flow characteristics specifications

% Comp. Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Compression

Compress the lubricated blend using punches mentioned in Table 6 and the tablet parameters are given in Table 7.

Table 6: Punches specification

Punch dimension	10.50 mm
Punch shape	Circular, Standard concave punches
Upper punch	Plain
Lower punch	Plain

Table 7: Tablet parameters as follows

Parameters	Specification
Description	Circular, biconcave, uncoated tablets, plain on both sides
Theoretical mass of tablet	500.00 mg
Average mass	500.00 mg ± 3.0 %
Uniformity of mass	NMT 2/20 ± 7.5% and none by ± 15.0 % mass.
Diameter	10.50 ± 0.20 mm
Thickness	5.30± 0.30 mm
Hardness	7-15KP/70-150 N
Friability	NMT 1.0 %m/m.

4.8. Evaluation of SR tablets

General appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

Size & shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by Vernier caliper or by other device. Tablet thickness should be controlled within a ± 7.5% variation of standard value.

Hardness

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength (Khemariya. P et al., 2010).

Friability

Friability of a tablet can determine in laboratory by Roche friabilator. This consist of a plastic chamber that revolves at 25 rpm, nearer to 6.5 grams of tablets are dropping through a distance of Six inches in the friabilator, which is then operate for 100 revolutions. The tablets are reweighed. Compress tablet that lose less than 0.1 to 0.5 % of the Tablet weigh are consider acceptable.

The percentage friability was measured by using the following formula

$$\% F = \{1-(W / W_o)\} \times 100$$

Where,

%F = friability in percentage

W_o = Initial weight of tablet

W = Weight of tablets after revolution.

Weight variation test

Take 20 tablets and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the U.S.P. test if not more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit (Pharmacopoeia of India, 1996).

Table 8: Limits of weight variation as per USP

Average weight of tablet (X mg)	Maximum % difference allowed
130 mg or less	10
130 mg to 324 mg	7.5
More than 324 mg	5

% Maximum positive deviation = $(W_H - A / A) \times 100$

% Minimum negative deviation = $(W_L - A / A) \times 100$

Where,

W_H = Highest weight in mg.

W_L = Lowest weight in mg.

A = Average weight of tablet in mg.

Drug content uniformity (Assay)

The formulated *Trimetazidine dihydrochloride* SR tablets were assayed for drug content.

Method

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 20 ml of methanol was added and then dissolve the substance and then sonicate for 15 min to get a clear solution, then make up to 100 ml with Phosphate Buffer pH 6.8 and then filter the solution through 0.45 µm filter and suitable dilutions were prepared with pH 6.8. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 231 nm by using UV-Visible spectrophotometer.

Calculation

Calculate the estimation of *Trimetazidine dihydrochloride* per tablet by using the formula:

$$\frac{\text{Test absorbance} \times \text{Standard weight (mg)} \times \text{Standard dilutions} \times 900 \times \text{Standard purity}}{\text{Standard absorbance} \times 100 \times \text{Test dilutions} \times \text{Lable claim}}$$

Dissolution (By UV Method)

Instrument **:** UV-spectrophotometer

Wave length : 231 nm

Dissolution parameters

Medium : Phosphate Buffer pH 6.8

Volume : 900 ml

Apparatus : USP Type-II (Paddle), with Sinkers.

RPM : 50

Time intervals : 1, 2, 4, 8, 12, 18, 21 and 24

Temperature : 37.0 ± 0.5°C

Sample preparation

Transfer one tablet into each dissolution bowels and run the dissolution apparatus as per dissolution parameters. Withdraw 10 ml of sample solution through auto sampler containing free flow filter, at the sampling time. Replace aliquots withdrawn for analysis with equal volumes of dissolution medium which is maintained at 37 ± 0.5°C.

Standard solution

Dissolve an accurately weighed quantity of *Trimetazidine dihydrochloride* 100 mg in 100 ml of Phosphate Buffer pH 6.8 (standard stock solution) separately, from this 10 ml of solution were pipette out and make up to 100 ml with Phosphate buffer pH 6.8 and the aliquot of concentration of 33 µg/ml was prepared and measured the absorbance at 231 nm by using UV visible spectrophotometer (Raj kumar et al., 2010).

Dissolution Medium

900 ml of Phosphate Buffer pH 6.8 (wipo patent application, 2009).

Buffer Preparation

Phosphate buffer pH 6.8

6.8 gm of Potassium dihydrogen ortho phosphate and 0.8 gm of sodium hydroxide pellets are added to 1000 ml of distilled water and adjust the pH with sodium hydroxide pellets.

Calculation

Calculate the % release of *Trimetazidine dihydrochloride* per tablet by using the formula:

Test absorbance X Standard weight (mg) X Sample dilutions X 900 X Standard purity

Standard absorbance X 100 X Test dilutions X Label claim

Table 9: Limits of *In Vitro* dissolution studies

Time (hrs)	Amount dissolved
2	NLT 25%
4	35-40%
8	50-60 %
12	60-70 %
18	80-90%
21	NLT 90%

The results of *in vitro* release profiles obtained for all the formulations were fitted into three models of data treatment as follows

1. Cumulative percent drug released versus time (zero-order kinetic model).

2. Cumulative percent drug released versus square root of time (Higuchi's model).

3. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

1. Zero order kinetics

A zero-order release would be predicted by the following equation.

$$A_t = A_0 - K_0 t \ldots 1$$

Where,

A_t = Drug release at time't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

2. Higuchi's Model

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\varepsilon/\tau(2A - \varepsilon C_s)\, C_S\, t]^{1/2} \quad \ldots 2$$

Where,

Q = Amount of drug released at time't'

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which 'Q' amount of drug is released.

Equation-2 may be simplified if one assumes that D, C_S and A are constant. Then equation-2 becomes:

$$Q = Kt^{1/2} \quad \ldots 3$$

When the data is plotted according to equation-3 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

3. Korsmeyer and Peppas model

The release rates from sustained release polymeric matrices can be described by the equation (4) proposed by Korsmeyer et al.

$$Q=K_1t^n \text{..... (4)}$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism.

For Fickian release, n=0.45 while for anomalous (Non-fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89 (Peppas, 1985).

***In- vitro* drug release studies for marketed product**

The in vitro drug release studies were performed for marketed product using dissolution medium as 6.8 pH Phosphate buffer volume 900 ml at 50 rpm, USP II apparatus. By using UV-spectrophotometer at 231 nm.

4.9. Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration for drug registration applications in the European Union, Japan and The United States of America.

ICH specifies the length of study and storage conditions

Table 10: Stability storage conditions

Study	Storage condition	Time period
Long term	25ºC ± 2 ºC/ 60% RH ± 5% RH	12 months
Intermediate	30ºC ± 2 ºC/ 65% RH ± 5%RH	6 months
Accelerated	40ºC ± 2 ºC/ 75% RH ± 5% RH	6 months

Stability studies were conducted according to ICH Guidelines; the optimized formulation was packed in Alu-Alu blisters and stored at three different conditions i.e. Long term, intermediate and accelerated conditions in a stability chamber for a period of 3months. The samples were evaluated for assay and dissolution studies at regular intervals.

5. RESULTS AND DISCUSSION

Trimetazidine dihydrochloride is a metabolic agent, acts at the cellular level to improve myocardial metabolism at the time of ischemia. In case angina pectoris *Trimetazidine dihydrochloride* increases coronary flow reserve, thereby delaying the onset of ischemia associated with exercise, limits rapid swings in blood pressure without any significant variations in heart rate, significantly decreases the frequency of angina attacks, and leads to a significant decrease in the use of nitrates. It improves left ventricular function in diabetic patients with coronary heart disease. Recently, it has been shown to be effective in patients with heart failure of different etiologies. Multiple dose administration at intervals of 6 to 8 hours is difficult for a patient with angina or a hypertensive patient. This can lead to patient non compliance.

Trimetazidine dihydrochloride with all evident advantages proved to be a suitable candidate for development of a sustained release dosage form. In the present study, HPMC K200M, Poly ethylene oxide WSR 301 and xanthan gum which are commonly used in hydrophilic matrix drug delivery systems, have been employed to formulate sustained release tablets of *Trimetazidine dihydrochloride*.

5.1. Preformulation Studies

Calibration graph

The Calibration Graph of *Trimetazidine dihydrochloride* performed in phosphate buffer pH 6.8. It shows regression value 0.999 so it passes linearity.

Table 11: Calibration curve data of *Trimetazidine dihydrochloride*.

Concentration(µg/ml)	Absorbance at 231nm
0	0
5.5	0.133
11	0.256
16.5	0.380
22	0.494
27.5	0.629
33	0.732

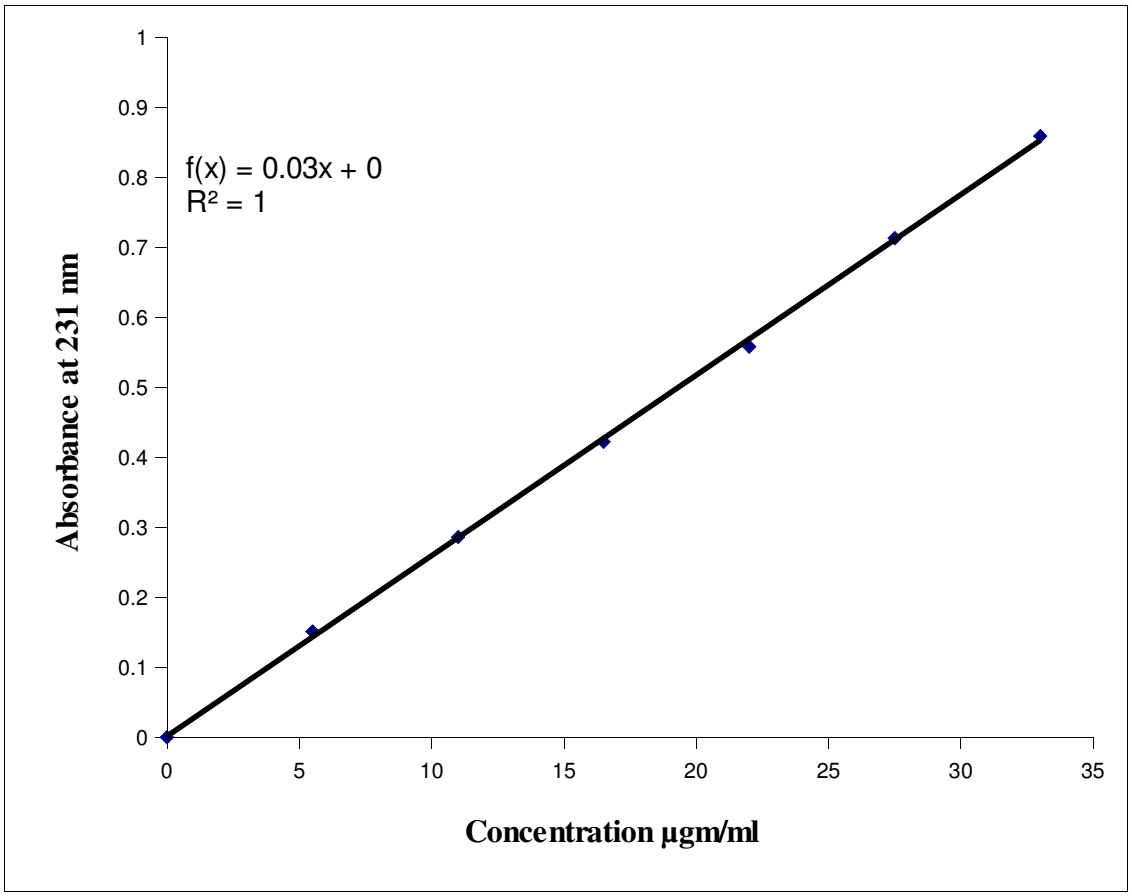


Figure 7: Calibration curve of *Trimetazidne Dihydrochloride* (pH 6.8)

5.2. Drug –polymer compatibility studies by FTIR

Figure 8: FTIR Spectra of *Trimetazidine Dihydrochloride.*

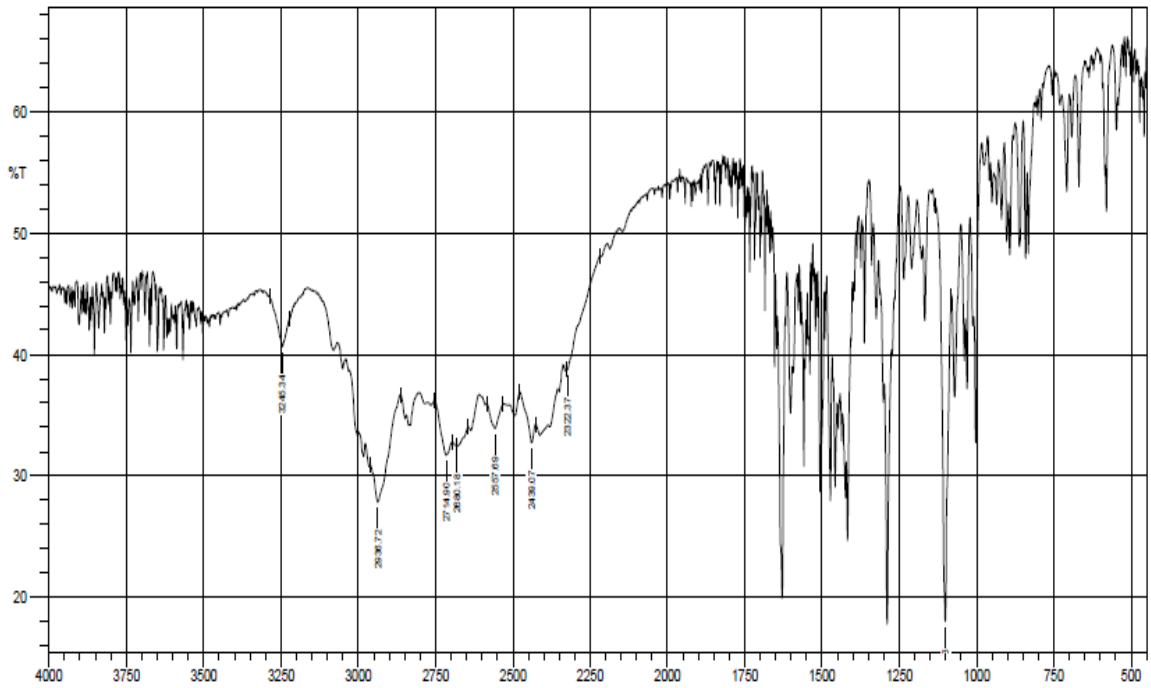


Figure 9: FTIR spectra of HPMC K200M.

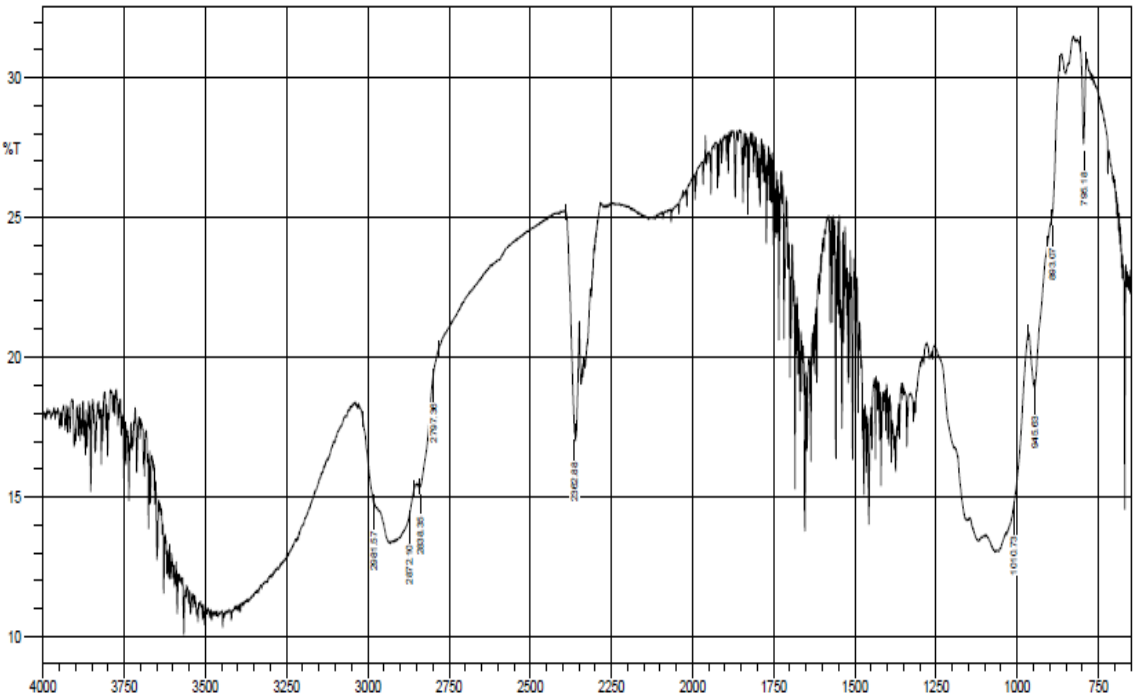


Figure 10: FTIR Spectra of Poly Ethylene Oxide WSR 301.

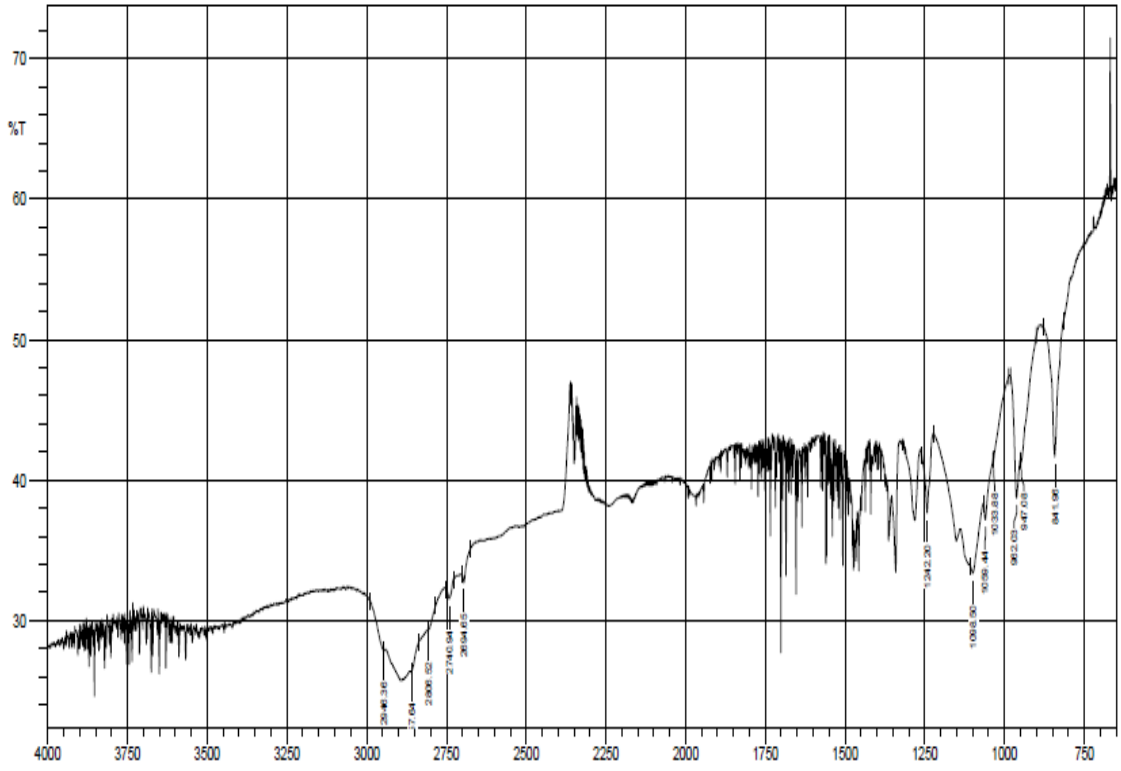


Figure 11: FTIR Spectra of Xanthan gum.

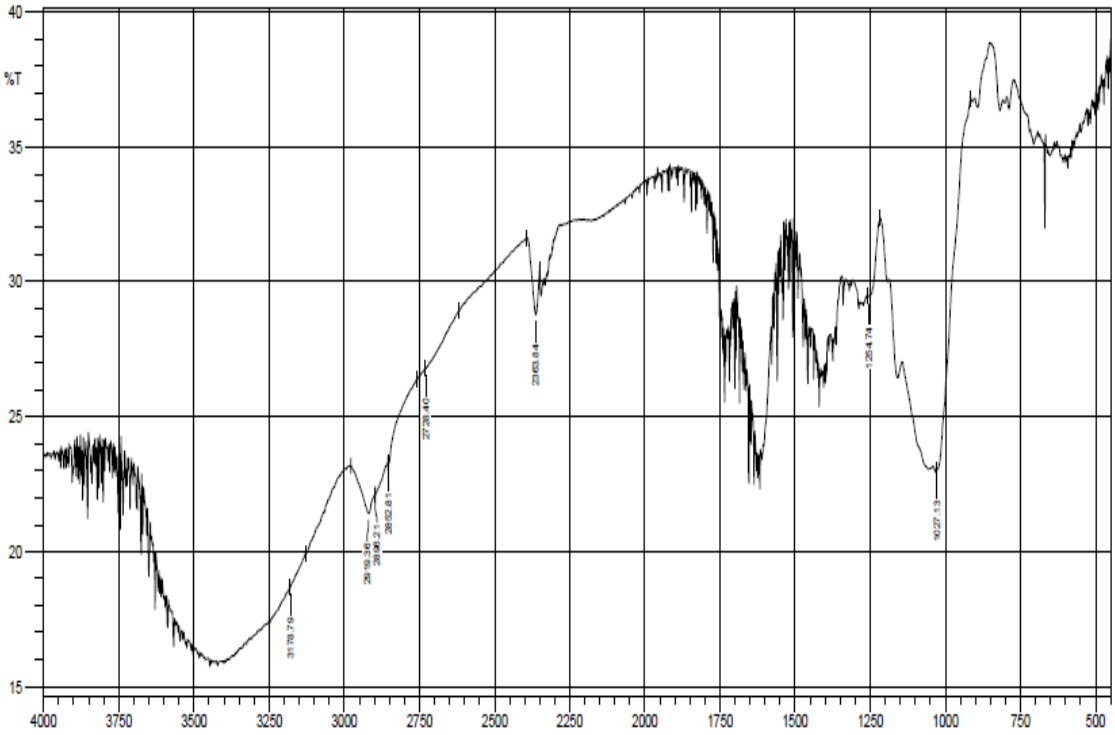


Figure 12: FTIR Spectra of *Trimetazidine dihydrochloride* and HPMC K200M.

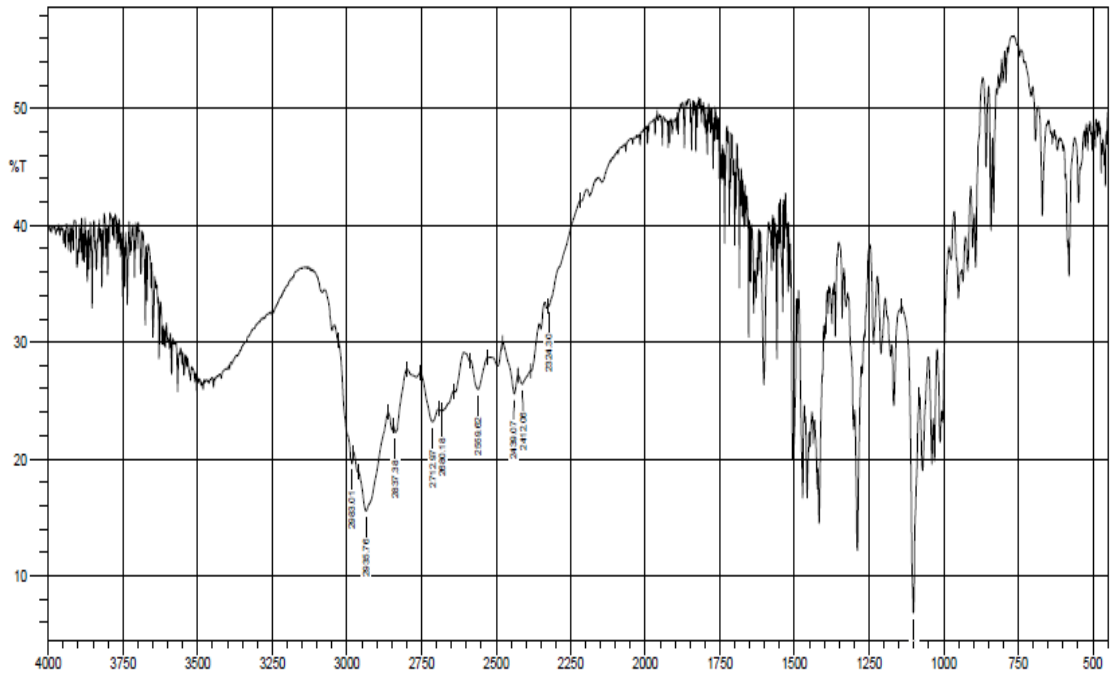


Figure 13: FTIR Spectra of *Trimetazidine dihydrochloride* & Polyox WSR 301.

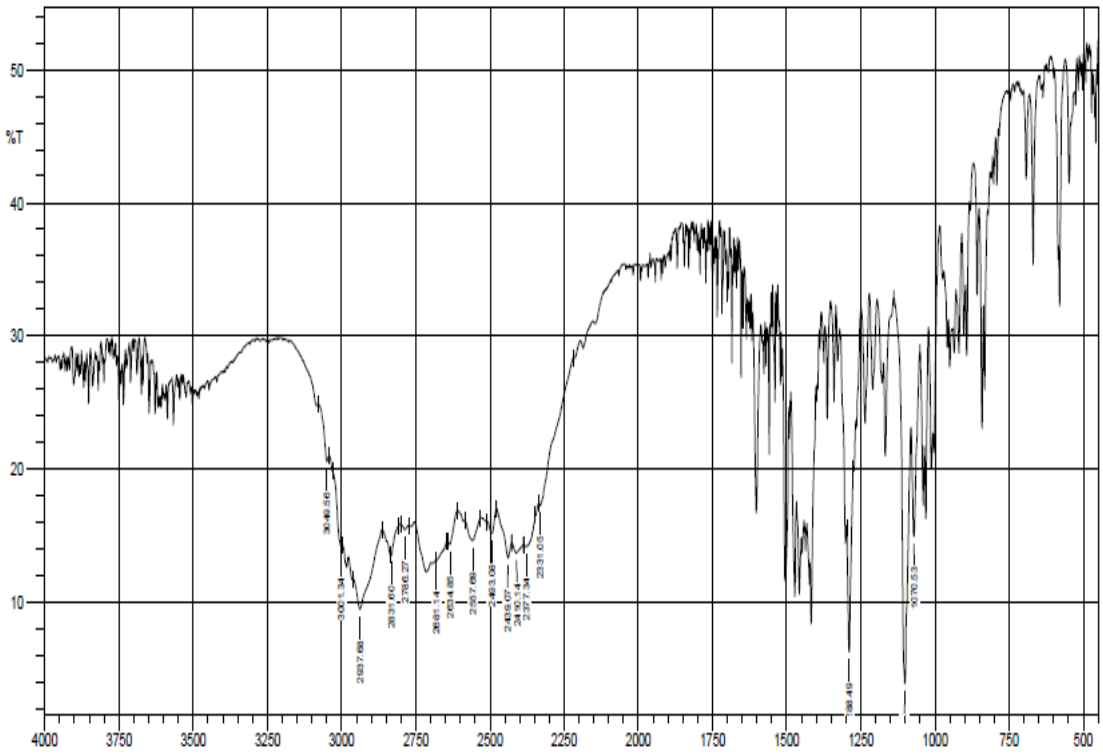


Figure 14: FTIR Spectra of *Trimetazidine dihydrochloride* and Xanthan gum.

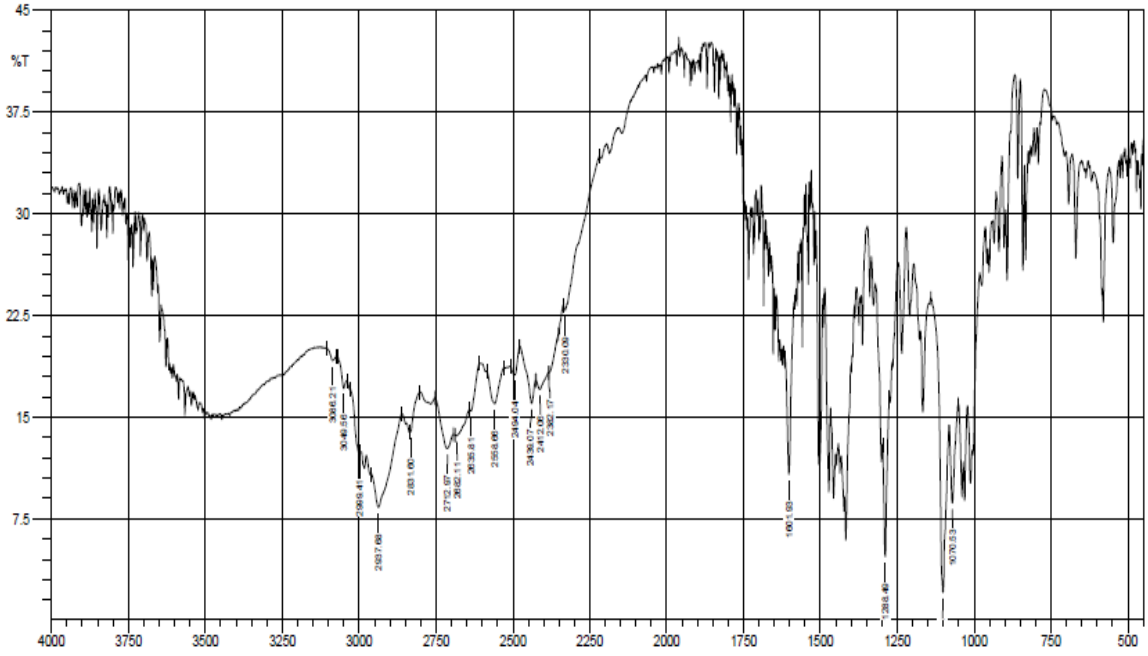
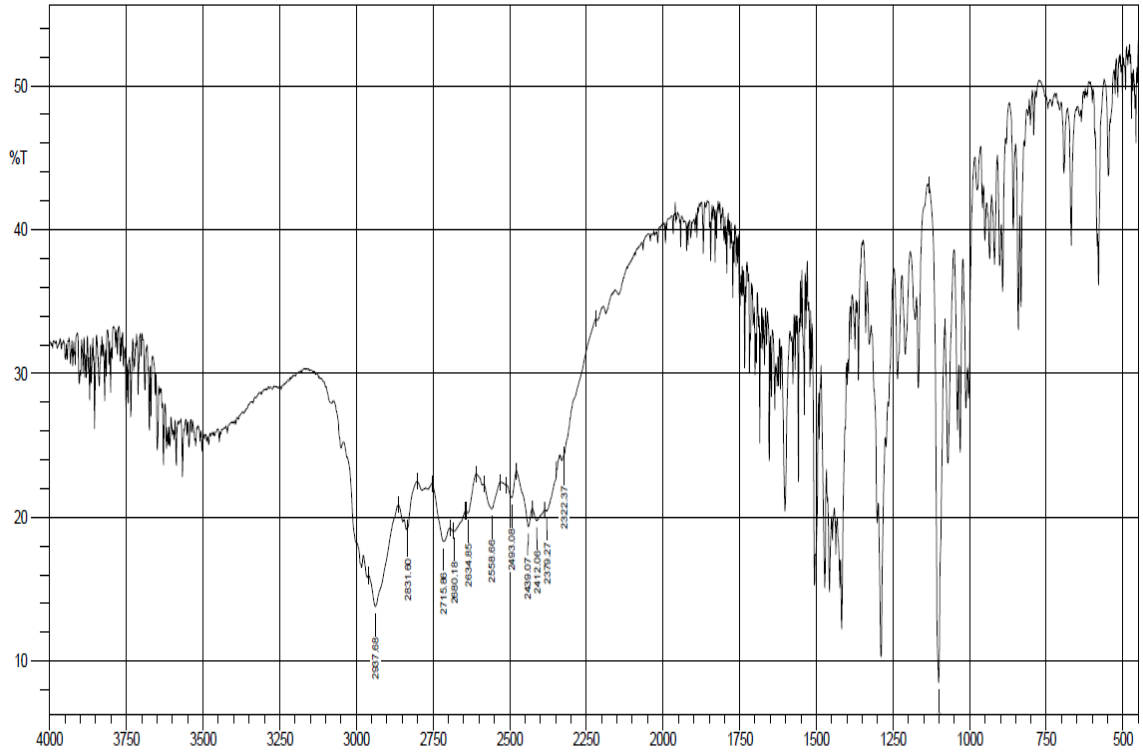


Figure 15: FTIR Spectra of *Trimetazidine dihydrochloride* and Placebo.



The FTIR spectra of Trimetazidine dihydrochloride, HPMC K200M, Poly ethylene oxide WSR 301 and Xanthan gum and the combination of drug and polymers were shown no significant interaction between drug and polymer. The FTIR spectra's of *Trimetazidine dihydrochloride*, HPMC K200M, Poly ethylene oxide WSR 301, Xanthan gum of drug along with polymers are shown in figures 8 to 15.

Trimetazidine dihydrochloride functional group characterstic peaks are observed in drug and with combination of polymers as shown in table 12 so it indicates there was no interaction between drug and other excipients.

Table 12: FTIR interpretation results for drug and polymers

S. No	Composition	Functional group ($\bar{v}$ in cm^{-3})			
		N-H(BN)	C-N(ST)	C=C(ST)	C-O(ST)
1	Characterstick peak	1650-1580	1340-1020	1600-1500	1260-1000
2	*Trimetazidine dihydrochloride*	1625	1285	1590	1100
3	API+HPMC k 200m	1610	1285	1589	1100
4	API+ Polyox WSR303	1612	1288.49	1595	1102
5	API+Xanthan gum	1601.93	1288.49	1505	1102
6	API+Placebo	1605	1288.49	1505	1102

5.3. Drug Excipient Compatibility studies by force degradation studies:

Compatibility studies at different temperature and relative humidity showed that drug itself was stable at higher temperature and relative humidity as well as compatible with all above used excipients.

Table 13: Drug excipient compatibility studies by forced degradation

Drug + Excipient	Initial	First month Observation		Comp atible
		25ºC/60%RH	40ºC/75% RH	
Drug	White Powder	No change	No change	Yes
Drug + HPMC	CreamyWhite	No change	No change	Yes
Drug + Polyox	White Powder	No change	No change	Yes
Drug + Xanthan gum	White Powder	No change	No change	Yes
Drug + DCP	White Powder	No change	No change	Yes
Drug + Povidone	White Powder	No change	No change	Yes
Drug + Silica	White Powder	No change	No change	Yes
Drug + Magnesiumstearate	White Powder	No change	No change	Yes

5.4. Evaluation Studies

Blend evaluation parameters

The flow properties and other derived properties evaluated for all 6 formulations were proved to be within limits showing good flow properties. The physical properties like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio were calculated and tabulated in table 14.

Table 14: Physico chemical parameters of blend

S No	Formulations	BD(gm/ml)	TD(gm/ml)	AR	CI	HR
1	F1	0.415	0458	24.51	12.5	1.09
2	F2	0.425	0.476	24.84	12.0	1.12
3	F3	0.416	0.476	27.96	14.4	1.14
4	F4	0.408	0.470	30.25	15.1	1.15
5	F5	0.402	0.465	30.01	14.9	1.14
6	F6	0.384	0.434	25.58	13.0	1.13
7	F7	0.370	0.430	28.17	16.2	1.16
8	F8	0.374	0.442	32.46	18.2	1.18

All values were average of 3

Physicochemical properties of tablets

The prepared Trimetazidine sustained release tablets were characterized based upon their physicochemical characteristics like thickness, weight variation, hardness, friability and drug content.

Weight variation

The weight variation of the tablet was found to be in the range of 497.5 mg to 504.6 mg. The Results were tabulated in table 16.

Thickness

The tablet thickness were observed by using digital vernier caliper and found to be in the range of 5.20 mm to 5.28 mm the results were observed in table 15.

Hardness

The difference in the hardness was affect the release of the drug from hydrophilic matrices which is 8.1 to 11.02 KP released by diffusion through the gel layer and/or erosion of this layer and is independent of the dry state of the tablet. The values were given in table 15.

Friability

Tablet strength was tested by Roche Friabilator. The friability of all formulations were observed within the range of 0.24% to 0.33%. The values were given in table 15.

Drug content

The Drug content of all formulations were observed within the range of 98.48% - 99.47% The values were given in table 15.

Table 15: Physicochemical parameters of *Trimetazidine dihydrochloride* ER tablet formulations.

Formulation	Thickness (mm)	Hardness (Kp)	Friability (%w/w)	Assay (%)	Meanweight (mg)	Standard deviation
F1	5.19	8.18	0.36	98.53	500.8	2.19
F2	5.20	8.10	0.33	98.48	500.67	2.21
F3	5.29	8.36	0.25	99.03	500.66	2.19
F4	5.22	8.96	0.26	98.66	500.05	2.14
F5	5.21	8.81	0.24	99.41	500.4	2.16
F6	5.25	9.16	0.25	99.47	500.8	2.18
F7	5.22	10.68	0.24	99.73	500.56	2.41

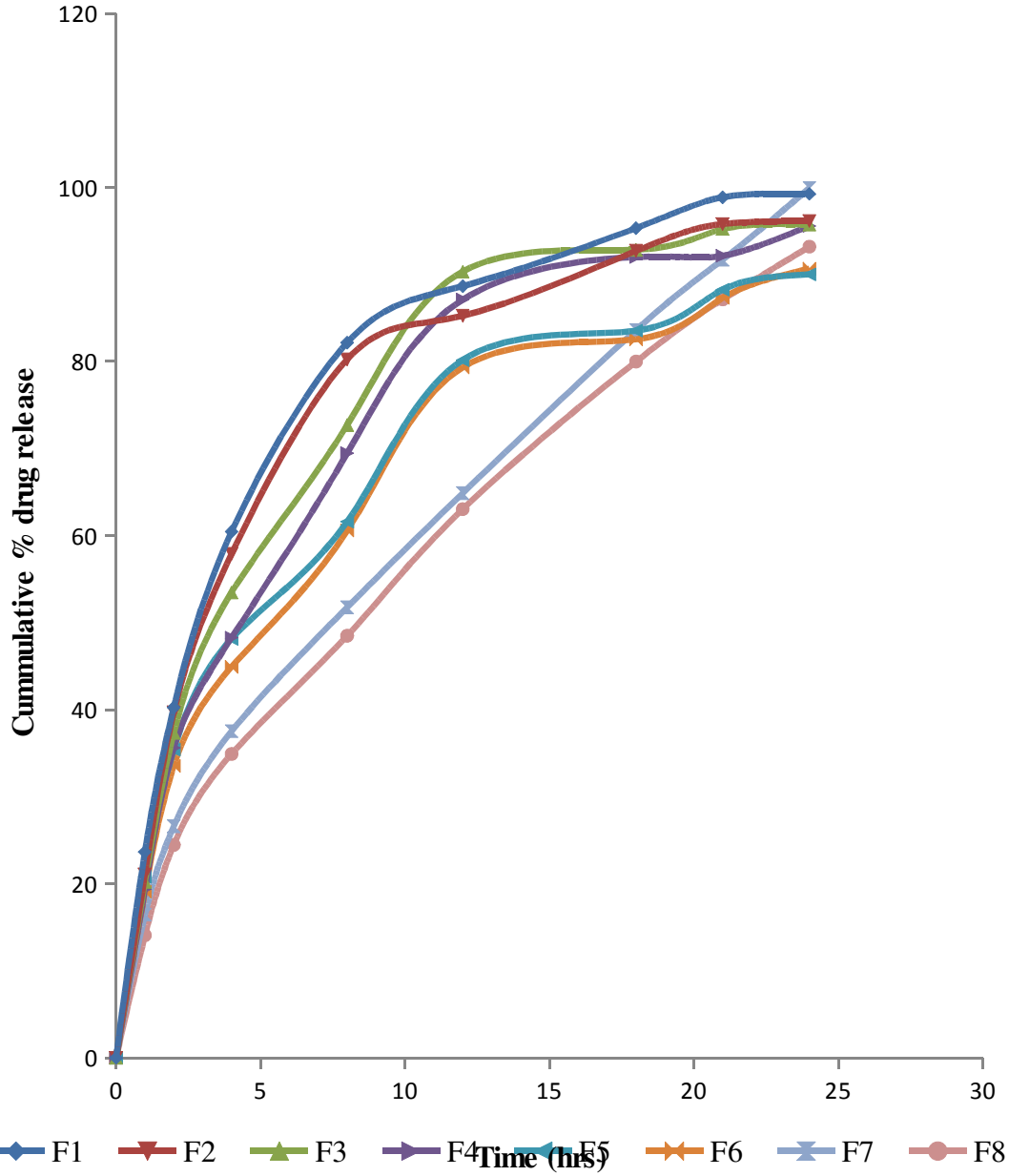
F8	5.28	11.02	0.25	98.49	500.45	1.99

***In-vitro* drug release studies.**

Table 16: *In-Vitro* Dissolution profile for *Trimetazidine Dihydrochloride* ER tablets of F1 to F8

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	23.645	21.07	20.22	19.39	20.82	19.08	16.45	14.08
2	40.25	39.71	37.32	35.62	35.41	33.53	26.59	24.46
4	60.43	57.89	53.46	48.26	48.15	44.91	37.52	34.91
8	82.15	80.23	72.69	69.45	61.58	60.56	51.75	48.49
12	88.65	85.25	90.31	87.09	80.15	79.31	64.86	63.03
18	95.31	92.69	92.82	91.99	83.54	82.54	83.59	79.98
21	98.85	95.78	95.20	92.13	88.25	87.29	91.68	87.12
24	99.25	96.12	95.72	95.56	89.99	90.64	99.89	93.18

Figure 16: I*nvitro* dissolution profile for Trimetazidine Dihydrochloride ER tablets for formulations: F1 to F8



Formulation of *Trimetazidine dihydrochloride* was prepared with polymers HPMC K200M, Ploy ethylene Oxide WSR 301 and Xanthan gum individually concentration of (2x and 3x) by direct compression technique. *In vitro* dissolution profile of HPMC K200M, Poly ethylene Oxide WSR 301 concentrations of (2x and 3x) the drug release was nearer to 97% at end of 8-12 hours, Xanthan gum showed the drug release was near to 95% 12-15 hrs.

Then formulations of *Trimetazidine dihydrochloride* were prepared with Poly ethylene oxide WSR 301: Xanthan gum and HPMC K200M: Xanthan gum combinations with different concentrations by direct compression technique. The formulation of F7 and 8 showed comparatively high hardness value of 10KP. This could be a presence of more concentration of HPMC K200M which is responsible for more hardness of the tablet. The low hardness value observed with formulation F1 and 2 due to the presence of less concentration of poly ethylene oxide WSR 301, which is generally decreases the hardness of tablet. Tablet hardness is not an absolute indicator of strength. Another measure of tablet strength is friability. All formulations showed less than 1% w/w friability that indicates the ability of tablets to withstand shocks which may encountered during transport. All the tablet formulations showed acceptable pharmacotechnical properties and compiled with In house specification for weight variation, assay, hardness and friability.

The *in vitro* drug release characteristics were studied in simulated gastric and intestinal fluid for a period of 24 hours using USP II dissolution apparatus. Initially tablets were prepared with a drug-polymer ratio of 1:1. But the tablets released 100% of *Trimetazidine dihydrochloride* within 3 hours. In an attempt to prolong the release of the drug, the concentration of polymer was increased. The tablets were prepared

with the ratio of 1:2 and 1:3. The drug release also 100% within 12 hours. Based on the results of *in vitro* dissolution, the tablets were prepared in combination of polymers.

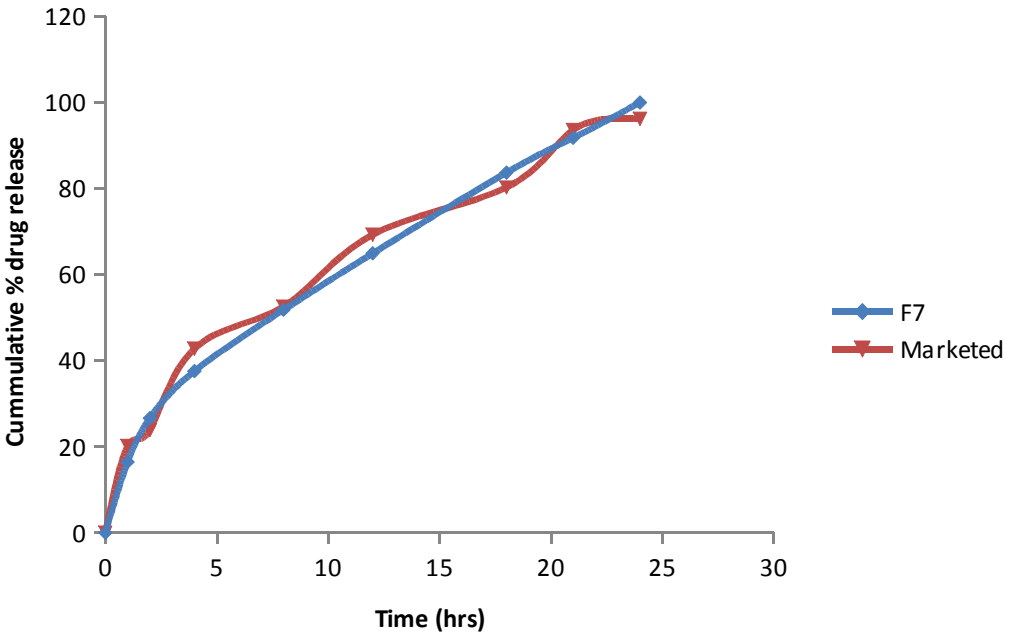
The drug was mixed with different proportions of Xanthan gum and Poly Ethylene Oxide WSR 301 and HPMC K200M. The 2x concentration of Xanthan gum was mixed with 1x, 2x, 3x and 4x concentration of Poly Ethylene oxide WSR 301. When the concentration of poly ethylene oxide increases it retards the drug release. The formulations were prepared with same concentration of Xanthan gum and low concentration of Poly ethylene oxide WSR 301 only retards the drug release. Firstly, the formulation F 1 was prepared with 2x:2x concentration of Xanthan gum and Poly ethylene oxide WSR 301, the tablets shown 85% of drug release with in 12hours. This is due to the less concentration of Poly ethylene oxide WSR 301. Secondly, F 2 was prepared with 2x:3x concentration of Xanthan gum and Poly ethylene oxide WSR 301, it shows drug release 92% within 18 hours. Third formulation was prepared with 2x:3x concentration of Xanthan gum and Poly ethylene oxide WSR 301, also shows like second these tablets showed 98% of drug release within 18 hours due to the high concentration of poly ethylene oxide. Next further 3 batches are prepared with same concentration of Xanthan gum and 2x, 3x and 4x concentration of HPMC K200M. The formulation F5 was showed that it releases the 87% of *Trimetazidine dihydrochloride* within 21 hours. Fifth formulation F7 was prepared with 2x:4x concentration of Xanthan gum and HPMC K200M , it shows the drug release 99% within 24 hrs and the blend of these formulation was showed good compressibility and flow properties. The formulation F 8 showed 93% of drug release at the end of 24 hours, this is due to the increased concentration of HPMC K200M and increased hardness of tablets.

The F1 to F3 showed slow release of *Trimetazidine dihydrochloride* in the initial hours then continuous shows barest release, which is probably due to faster dissolution of highly water soluble drug from core and its diffusion out of matrix forming the pores for the entry of solvent molecules. Among all these formulation, the F3 showing 25-30% of drug release within 2 hours and 99% of drug release at the end of 24 hours. This formulation can be considered as a successful formulation since they showed little deviation from the theoretical release pattern throughout the dissolution period.

Table 17: *In-Vitro* drug release for marketed product

S. NO	Time (hrs)	Marketed product (%)
1	1	20.12
2	2	23.84
3	4	42.74
4	8	52.51
5	12	69.19
6	18	80.16
7	21	93.51
8	24	96.07

Figure 17: Comparison of *in vitro* drug release profile for marketed0 product & Optimized formulation F7



***In-vitro* release kinetics**

Data of *in vitro* drug release were fit into different equations and kinetic models to explain the release kinetics of Trimetazidine from the sustained release tablet. The kinetic models used were a Zero-order equation, Higuchi's model and Peppa's models. The obtained results in these formulations were plotted in various model treatment are as follows. I.e. Cumulative percentage drug release Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppa's). To know the mechanism of drug release from sustained release tablet, the drug release data was fit into Higuchi's models.

Mechanism of drug release

To find out the mechanism of drug release from hydrophilic matrices, the *in vitro* dissolution data of each formulation with different kinetic drug release equations. Namely Zero order: $Q=K_0t$; Higuchi's square rate at time: $Q=K_Ht^{1/2}$ and Peppa's: $F=K_mt^n$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geometric and structural characteristic of tablet and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (R) indicate the kinetic of drug release was zero order and the mechanism of drug release by Peppa's model indicates the non fickian evidenced with diffusion.

Table 18: *In-Vitro* drug release kinetics for optimized formulation: F7

***Zero order* data**		**Higuchi's data**		**Peppa's data**	
Time (hrs)	**Cumulaive. % release**	$\sqrt{T}$	**Cumulative. % release**	**log time**	**log cumulative. % release**
0	0	0	0		
1	16.45	1.00	16.45	0	1.2
2	26.59	1.41	26.59	0.34	1.42
4	37.52	2.00	37.52	0.60	1.57
8	51.75	2.83	51.75	0.90	1.71
12	64.86	3.45	64.86	1.07	1.81
18	83.59	4.24	83.59	1.25	1.92
21	91.68	4.58	91.68	1.32	1.96
24	99.89	4.90	99.89	1.38	1.99

Figure 18: Zero order plot for optimized formulation F7

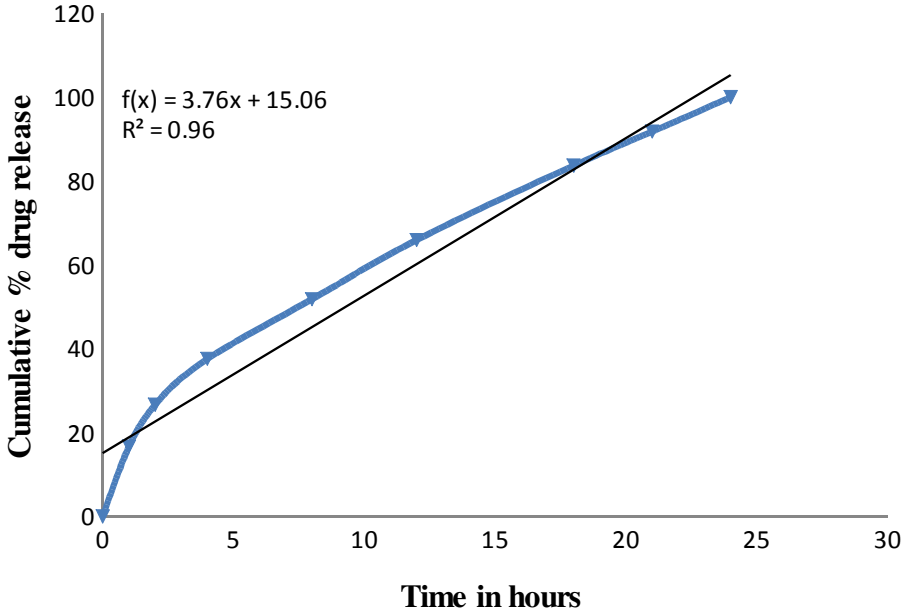


Figure 19: Higuchi's plot for optimized formulation: F7

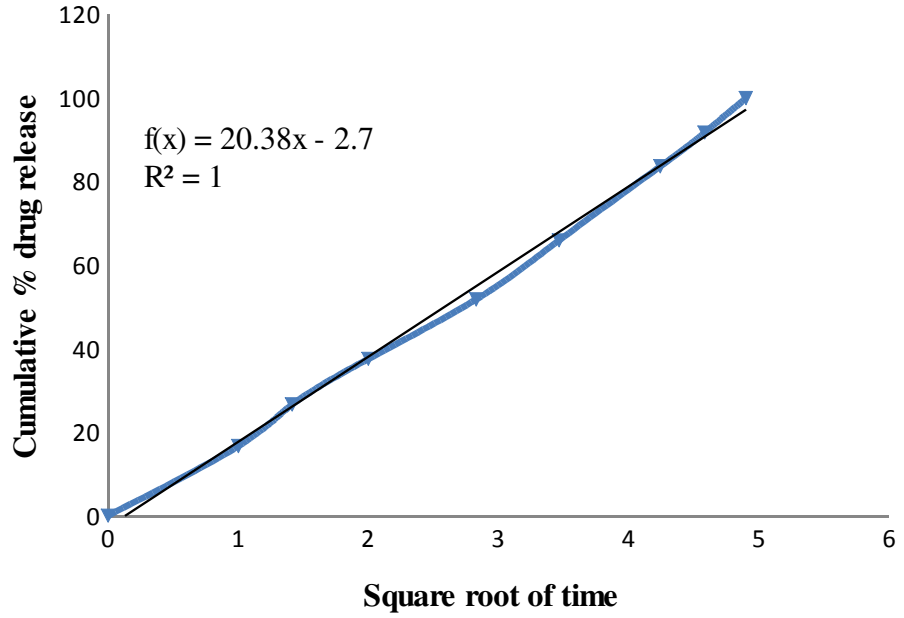
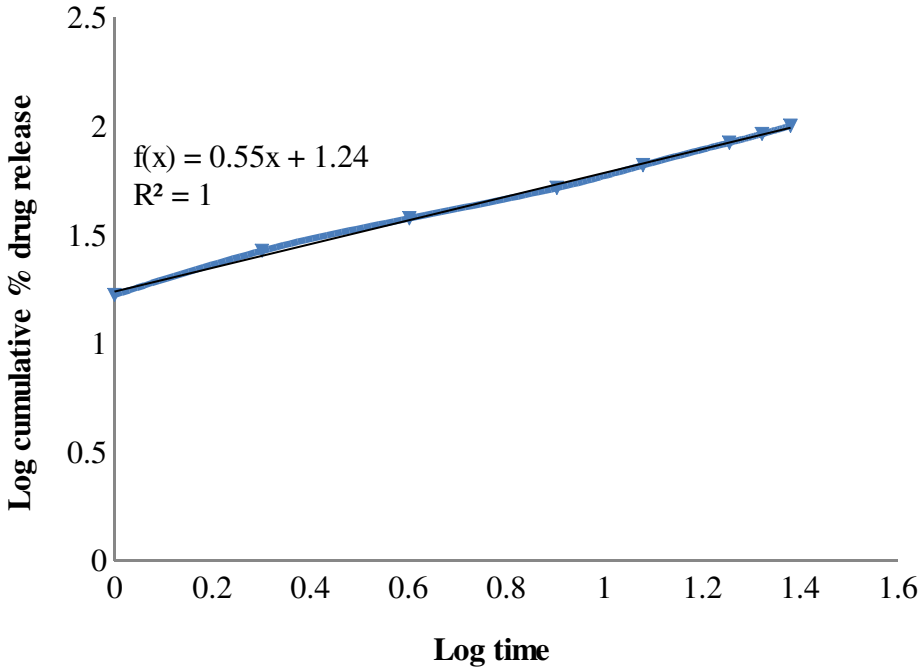


Figure 20: Peppa's plot for optimized formulation F7



5.5. Stability studies

The stability studies were carried out according to ICH guidelines for optimized formulation i.e. F7. The stability studies were carried out under 3 conditions i.e. Long term stability (25±2^{0}C/60% ±5% RH),Intermediate(30±2^{0}C/65% ±5%)and Accelerated stability studies (40±2^{0}C/75% ±5% RH). The tablets were packed in Alu-Alu blister packing. Then tablets were stored under 3 conditions and the tablets were withdrawn at every one month and evaluate the tablet parameters like description, assay and dissolution.

Sample were collected at an interval of 1,2 and 3rd months and evaluated. Discription, Assay and dissolution profile of F7 stored at three conditions in 1M, 2M and 3M samples was found to be similar with that of initial samples.

Table 19: Physical evaluation of stability studies for optimized formulation (F7)

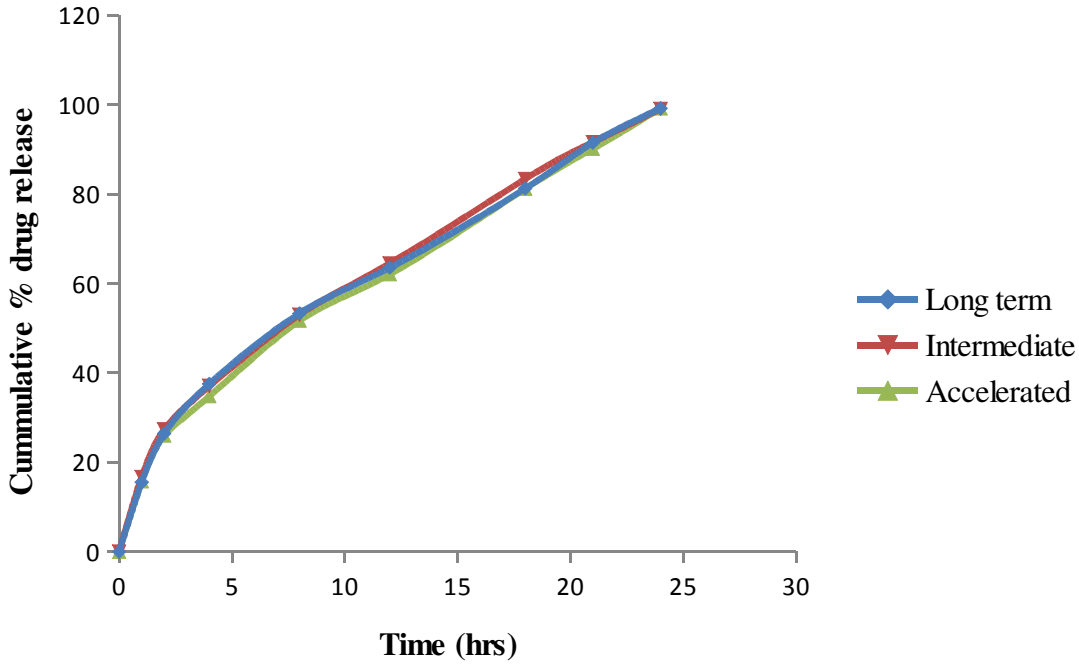
At 3 different conditions carried out for 3 months duration.

	Description	**Month**	**Cummulative % drug release (time in Hrs)**
T	White to off white color		
2	White to off white color		

Test									
		1	**2**	**4**	**8**	**12**	**18**	**21**	**24**
Long -term	1	16.57	26.68	37.12	52.9	63.33	82.86	91.76	99.23
	2	16.7	26.87	37.0	52.62	64.08	82.61	92.15	99.13
	3	15.52	26.41	37.55	53.31	63.54	81.26	91.48	99.19
Inter- mediate	1	15.45	26.75	36.95	53.47	64.09	83.19	91.55	99.33
	2	16.82	27.02	36.25	52.89	64.34	82.33	91.97	99.67
	3	16.72	27.35	37.07	53.02	64.48	83.39	91.62	99.08
Accel- erated	1	15.48	26.92	37.08	52.74	63.43	82.32	92.31	99.48
	2	16.91	25.99	35.63	54.24	64.24	82.94	91.12	99.81
	3	15.7	25.98	34.77	51.70	62.08	81.18	90.16	99.15

Table 20: Cummulative percentage release of stability studies of optimized formulation (F7) at 3 different conditions carried out for 3 months duration.

Figure 21:*In Vitro* Dissolution study for optimized formulation (F7) at 3 different conditions (after 3 month).


120
100
80
60
40
20
0
Cummulative % drug release
0
5
10
15
20
25
30
Time (hrs)
Long term
Intermediate
Accelerated

6. SUMMARY & CONCLUSION

- The present study was carried out to develop *Trimetazidine dihydrochloride* modified release matrix tablets in combination of three hydrophilic polymers for safe and effective action. Matrix tablets with HPMC K 200, Xanthan gum, Povidone were prepared by direct compression method and evaluated. Matrix is also done in order to achieve the release of drug as per expectation.

- The FT-IR spectroscopy study was carried out to know the preformulation and Compatibility of the excipients with *Trimetazidine dihydrochloride*, the active constituent of the formulation. Results were found no significance changes in characteristic peaks of drug in the recorded IR spectrum. These preformulation and compatibility study were confirmed the drug and other excipients in the formulation are compatible with each other.

- The Matrix tablets were prepared by Direct Compression Method. The angle of repose of the powder mixture was found to have 25 to 32. The flow property of the powder was excellent that was confirmed by the determination of angle of repose which indicates better uniformity of weight. Compressibility index (%) of formulations was observed between 12.782% to 18.252% that showed excellent compresibility.

- The matrix tablets were compressed by applying maximum force of compression and the hardness of tablets was found to be in the range of 8 Kp to 11 Kp. Appreciable hardness of the matrix tablets indicated retardation in the release as observed in dissolution profile.

- The release of F1 and F2 were not sustained the release of the drug and results were found upto drug released 82.13% and 81.47% within 8 hours respectively. Formulations F3 and F4 showed the drug release 92.41% and 91.93% in 18 hours respectively, which indicates that by increasing the concentration of polyox the drug release was sustained. The release rates was sustained in formulations F1 to F4 but drug release pattern was not close to theoretical release profile.

- The formulation F5 (drug & polymer 1:1) showed the drug release 80.93% for 12 hours, in order to minimize the retardation of drug release ratio of HPMC was increased to twice and the drug release was 79%, in formulation F6. Then in order to achieve better release drug by change the proportional (ratio) of both polymers. The formulation F7 has showed 99.89% drug released for 24 hrs on increasing the concentration of polymer in the ratio of 1:3.

- Satisfactory descriptions of kinetic model of the formulations were found good according to higuchi's kinetic model. The ideal properties of matrix tablets are sufficient release of drug in pH 6.8 phosphate buffer solution, so it was necessary to select an appropriate drug release between HPMC and Polyox. The formulation F7 found to be best.

- The comparative study were performed between my optimized formulation F7 Vs Marketed product (Cardimax), were found to be better control of drug release F7 showed 99.89% and marketed product showed 96.07% at 24 hours *In-Vitro* release studies.

- Stability studies were carried out for optimized formulation F7 were showed no significance changes in physical parameters. Stability studies are carried out for 3 months at three different conditions (Long term, intermediate, accelerated) in various storage conditions. Also there was no remarkable change in the content of matrix tablets.
- Hence it can be concluded that once daily extended release matrix tablet of *Trimetazidine dihydrochloride* having satisfactory extended release profile which may provide an increased therapeutic efficacy. The developed formulation overcome and alleviates the drawback and limitation of extended release preparations.

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